

Studies Towards the Synthesis of Frog Alkaloid 251F

By

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DECLARATION

I hereby certify that this research is a result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed.....

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I hereby certify that this statement is correct

Signed.....

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February 2004

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ABBREVIATIONS

Ac	acetate
a.m.u.	atomic mass units
Ar	aryl/aromatic
ArSO ₂ N ₃	<i>para</i> -nitrobenzenesulfonylazide
b.p.	boiling point
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BF ₃ ·OEt ₂	boron trifluoride diethyl etherate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
BsCl	benzenesulfonyl chloride
Bu	butyl
BU ₄ NI	tetrabutyl ammonium iodide
BU ₃ P	<i>n</i> -tributylphosphine
<i>ca.</i>	approximately
CDCl ₃	deuteriochloroform
(CH ₃) ₃ NO	trimethylamine <i>N</i> -oxide
CO	carbonyl
conc.	concentrated
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl 1,3-acetonedicarboxylate
DET	2,5-diethoxytetrahydrofuran

DMS	dimethylsulfide
DMSO	dimethylsulfoxide
ed.	Editor
ee	enantiomeric excess
Et	ethyl
Etl	ethyl iodide
<i>etc.</i>	<i>etceteras</i>
EtOAc	ethyl acetate
eV	electron volts
GC-MS	gas chromatography mass spectroscopy
HOMO	highest occupied molecular orbital
<i>i</i>	iso
<i>i.e.</i>	that is
(<i>i</i> -PrO) ₄ Ti	titanium tetraisopropoxide
IR	infrared
J	coupling constant
Kcal/mol	kilocalories per mole
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazane
LDA	lithium diisopropylamine
LiHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazane
LUMO	lowest unoccupied molecular orbital
m	multiplet
Me	methyl
MeMgBr	methyl magnesiumbromide
m.p.	melting point

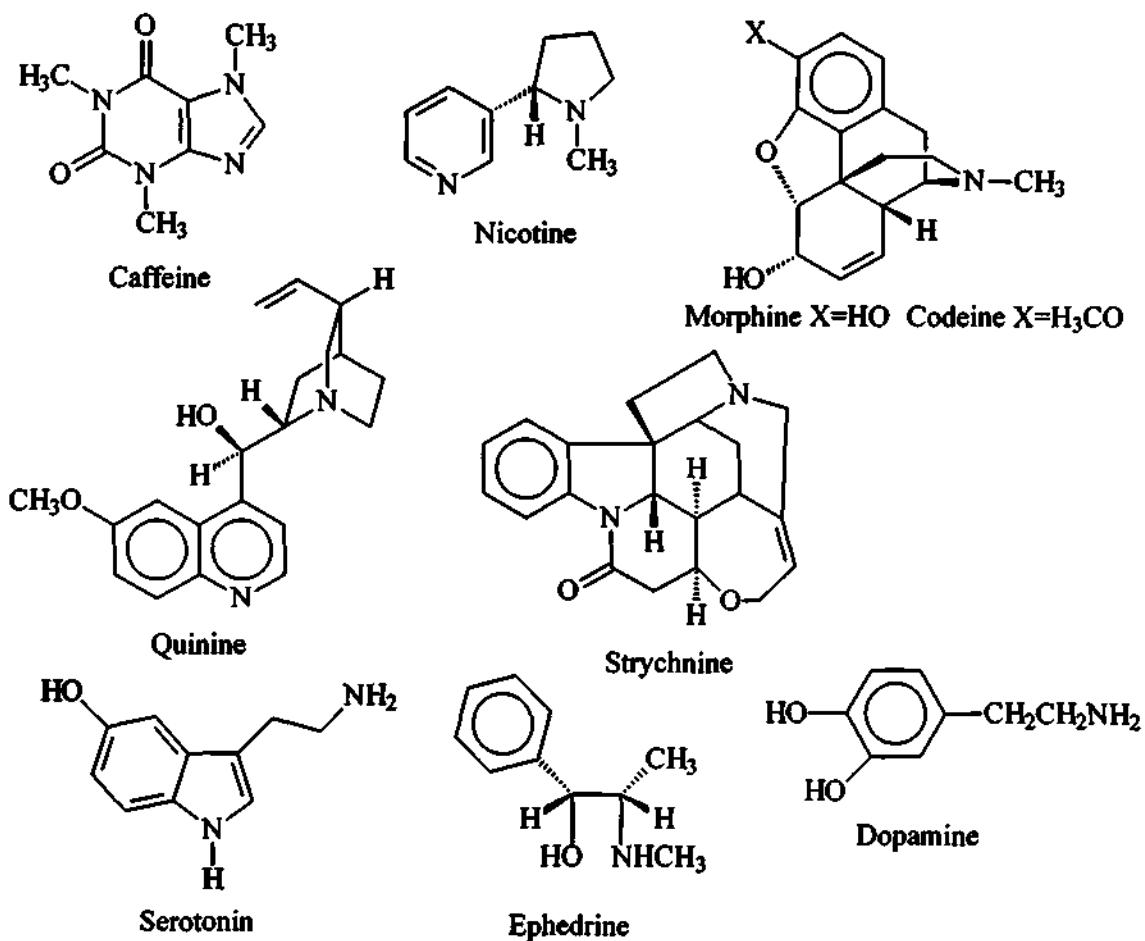
MW	molecular weight
NaOEt	sodium ethoxide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NaN ₃	sodium azide
Ph	phenyl
PhS ₂	phenyl disulfide
ppm	parts per million
Pr	propyl
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
py	pyridine
q	quartet
Rh ₂ Oct ₄	rhodium octanoate
rt	room temperature
s	singlet
t	triplet
<i>t</i>	tertiary
<i>t</i> -BuOOH	butyric acid
TEA	triethyl amine
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS-	trimethylsilyl
TsCl	toluenesulfonyl chloride
Zn(N ₃) ₂ ·2pyr	zinc diazopyridine

CHAPTER 1

INTRODUCTION

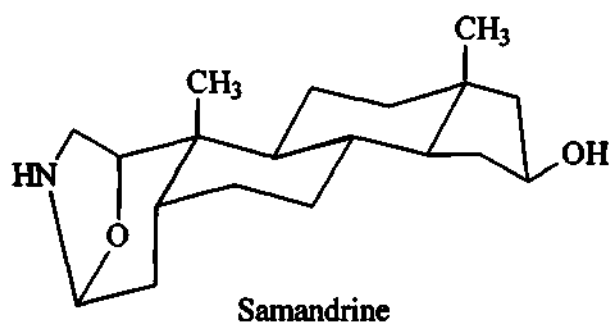
1.1 A Brief Introduction to Alkaloids

Alkaloids are a class of natural products whose discovery and use parallel civilization itself. Their biological activity has made them valuable pharmaceutical agents. The alkaloids with which we are most familiar with are those such as caffeine, nicotine, morphine, quinine, strychnine, serotonin, codeine, ephedrine (adrenaline) and dopamine. Alkaloids have been isolated from a wide variety of natural sources. The majority of the



over 5000 alkaloids that are known have been isolated from plant sources but mammalian, arthropod, marine, fungal and bacterial sources have proved invaluable in providing a rich library of these compounds.¹ The word “alkaloid” was coined by the pharmacist W. Meissner in 1819, and simply meant “alkalilike”.¹ This was because all alkaloids at the time were basic, nitrogen containing compounds. However, the sheer diversity of the structures that are classified as alkaloids has precipitated the adoption of a rather general definition which states “an alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms”.¹

As mentioned previously, originally alkaloids were regarded as basic compounds derived from plant sources, with alkaloid-type structures only rarely found in animals.¹ During the last three decades the situation has changed with the isolation of dozens of alkaloids from animal sources.¹ The first genuine example of an alkaloid isolated from an animal source was that of “samandarine”, which was isolated in 1866, from an amphibian, the European fire salamander (*Salamandra maculosa* Laurenti).¹ Samandrine is a relatively potent neurotoxin, which is centrally active.¹

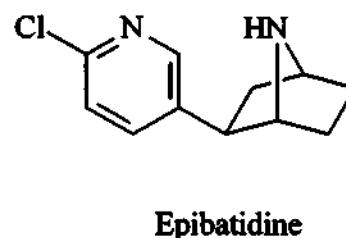
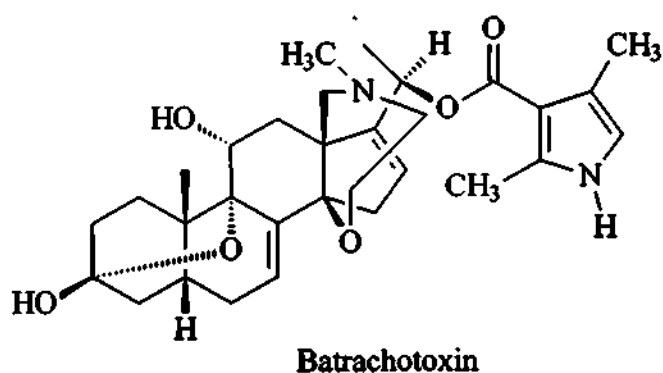


Toxic alkaloids occur not only in salamanders but also in particular terrestrial frogs and tree frogs. The skins of several varieties of the brightly coloured terrestrial frogs and tree frogs native to Colombia contain a lethal venom.¹ The Chocó Indians of Colombia use these frogs to poison the arrows of their blow darts for hunting.² The frogs are used in

different ways depending on the potency of their venom. The frogs are impaled on a stick and sometimes held near a fire so that the frog secretes a white froth of poison.³ The point of the arrow is then rolled or dipped in the venomous secretion to poison the arrow.³ Some frogs like *Phyllobates terribilis* are so toxic that the Chocó Indians simply rub the arrow on the frog's back and it will remain lethal for a year!³ The amphibian family *Dendrobatidae* has been the source of over 100 alkaloids which are exclusive to this family of neotropical frogs.⁴

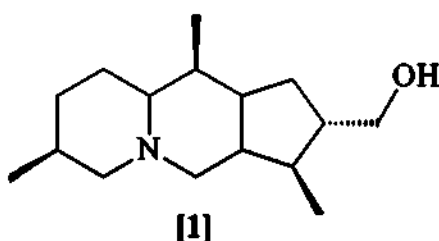
1.1.1 An Overview of the Dendrobatid Alkaloids

Amphibian skins have provided many biologically active compounds.⁵ The Dendrobatid frogs of Central and South America have proved a rich source of such compounds comprising over 20 structural classes.⁶ Such compounds serve as a chemical defense against predators.⁷ The so-called poison frogs of the family *Dendrobatidae* have bright colouration and distinctive patterns to "warn" predators that these frogs are distasteful and potentially lethal.⁷ However, there appear to be many mimics that prosper from "false warnings" too.⁷ Interestingly, it has been shown from feeding experiments and rearing these frogs in captivity that they do in fact not synthesize any alkaloids *de novo* from precursors, but instead they possess developed or over-expressed systems that accumulate the alkaloids from dietary sources.⁸ For dendrobatid frogs this diet consists of small and even tiny arthropods such as mites, ants, springtails and flies.⁸ These alkaloids are then stored, unchanged, in the glands of the skin.⁸ The dendrobatid alkaloids, as a class of natural products, possess a variety of biological activities: examples being batrachotoxin⁹ that is an agonist of voltage-dependent sodium channels, and epibatidine¹⁰ that is a potent analgesic.



1.1.2 Isolation and Characterization of Dendrobatid Alkaloid 251F

Daly and Spande isolated a unique alkaloid, 251 F [1], from the skin extracts of two populations of the dendrobatid frog *Minyobates bombetes* in 1992.¹¹ Alkaloid 251F



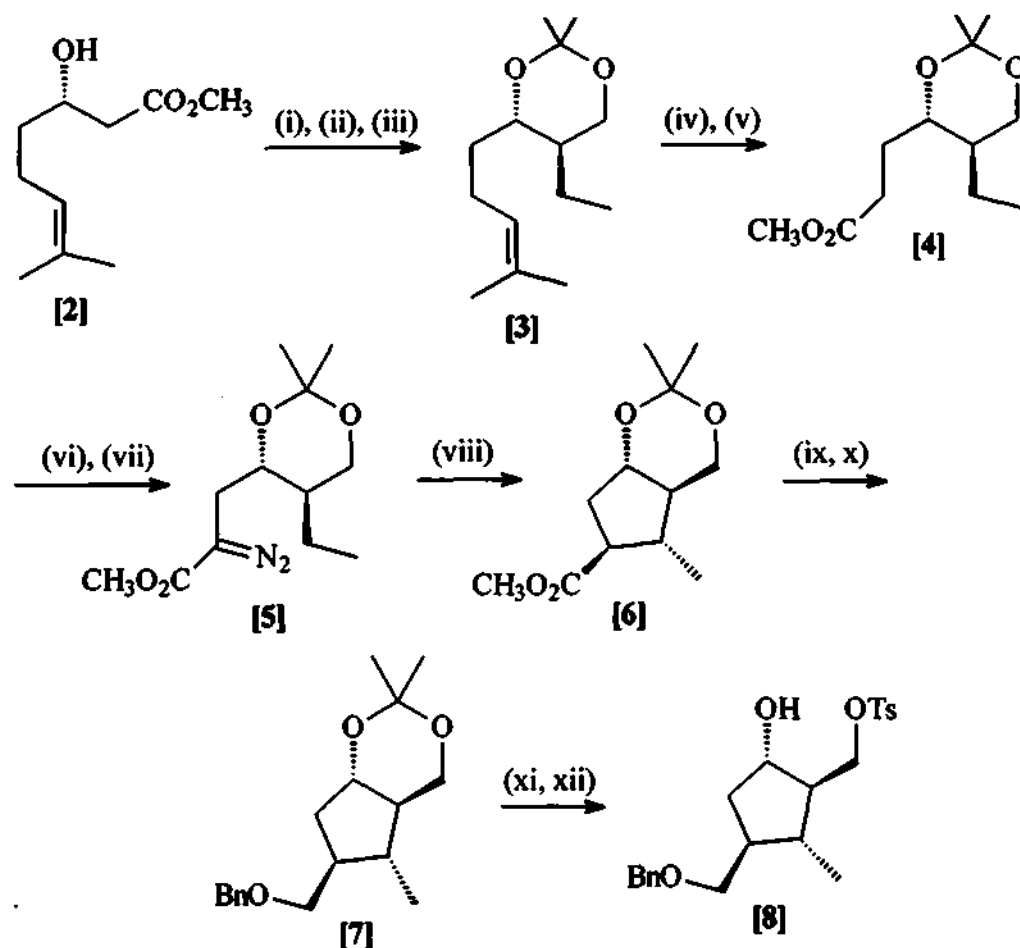
possesses a cyclopentaquinolizidine tricyclic skeleton.¹¹ This alkaloid is the parent member of the cyclopenta[*b*]quinolizidine alkaloids that are unique structural motifs as they are found nowhere else in Nature.¹¹ Neither the biological activity, nor the absolute stereochemistry of the alkaloid has been investigated because too little natural material has been isolated.¹¹ In 1992 only 340 µg of alkaloid 251F was isolated by chromatography and exhaustive MS and NMR analysis led to the determination of the structure.¹² Hence the important need to devise synthetic methods to make more of this natural product.

1.2 Reported Total Syntheses of Dendrobatid Alkaloid 251F

To date only two total syntheses of alkaloid 251F have been reported: the first by **Taber and You** in 1995¹³, and the second by **Sahasrabudhe, Aube and Wroblewski** in 2002.¹⁴ A convergent synthesis was used by **Taber and You**.¹³ This approach involves synthesising separate fragments of the molecule, from which the target molecule is assembled near completion of the synthesis. In contrast, the synthesis by **Sahasrabudhe, Aube and Wroblewski**¹⁴ is a linear synthesis, where the process begins with a single starting compound and eventually yields the final product.

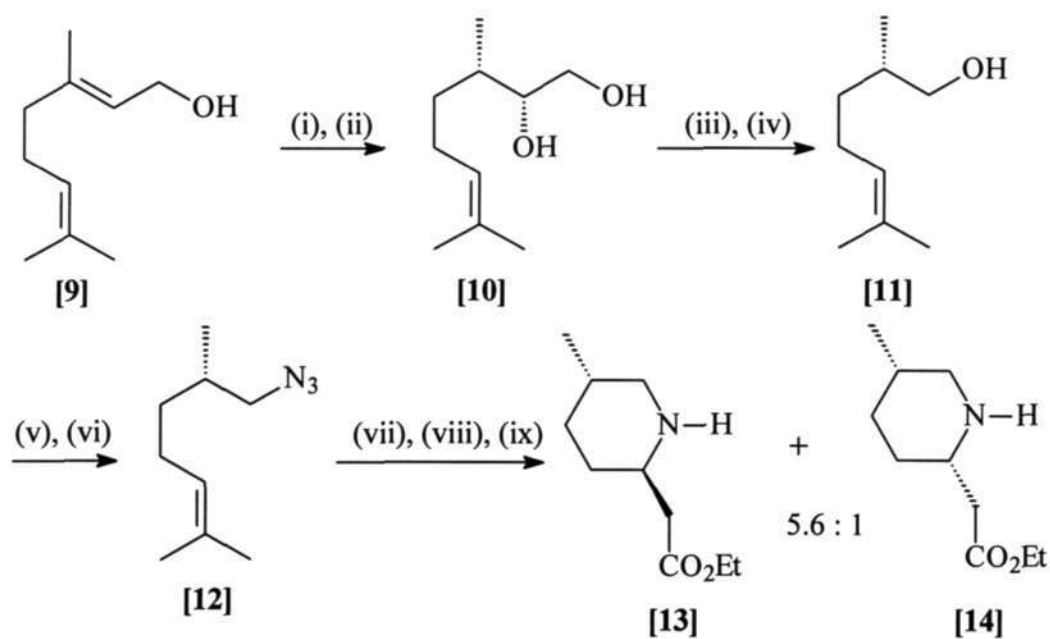
Taber and You¹³ published the first total synthesis of dendrobatid alkaloid 251F in 1995. Thanks to this enantioselective synthesis the structure of alkaloid 251F was finally confirmed.¹³ In this convergent synthesis the most important features are the Rh-mediated and anionic cyclisations that proceed with excellent diastereoselectivity. First 6-methyl-5-heptene-2-one [**Scheme 1.1**] is converted into a β -ketoester and hydrogenated by Ru BINAP to afford **[2]**.¹⁵ The dianion was then alkylated to give the anti-product which was then reduced and protected to yield **[3]**. Ozonolysis of alkene **[3]** was then followed by oxidation¹⁶ and conversion to methyl ester **[4]**. Diazo transfer of this ester **[4]** produced the diazoester **[5]**. Rh-mediated cyclisation was performed to yield **[6]** as the only diastereomer (4*aR*, 5*R*, 6*S*, 7*aR*). Reduction of ester **[6]** and subsequent protection of the primary alcohol as a benzyl ether led to **[7]**. Chemoselective monotosylation of the derived diol then yielded **[8]**. This process took 12 steps and produced **[8]** in an overall yield of 12% from **[2]**.

In order to achieve a convergent assembly of the alkaloid **[1]** large quantities of enantiomerically pure piperidine **[13]** needed to be prepared [**Scheme 1.2**]. This was done by performing a Sharpless asymmetric epoxidation¹⁷ on geraniol **[9]**. After the Hutchins

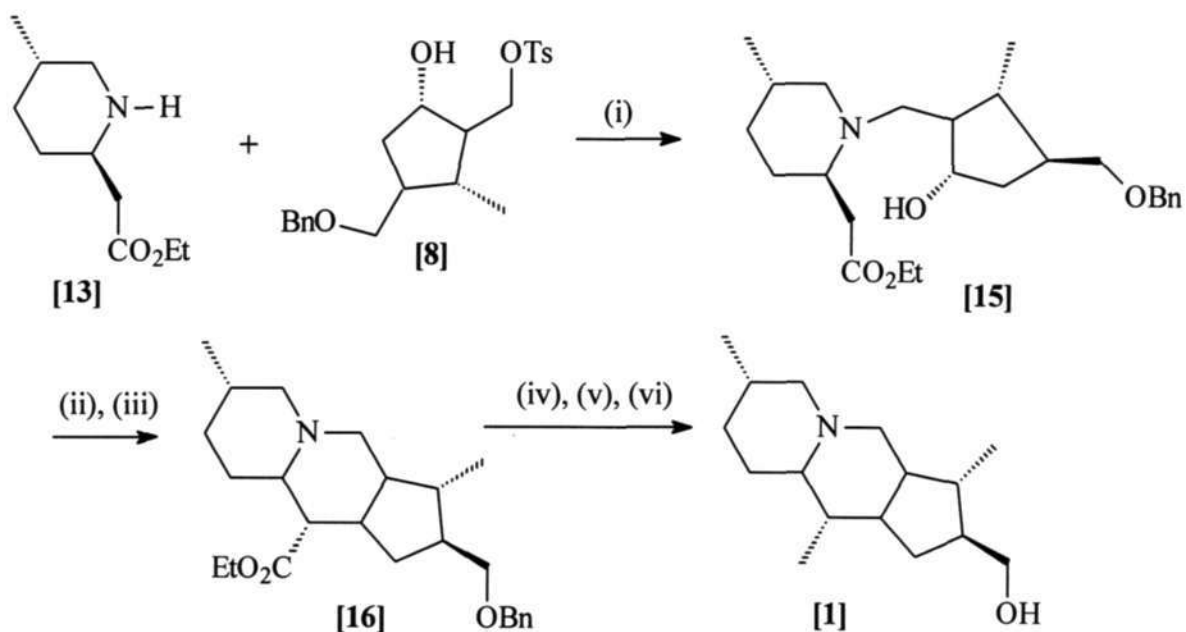


Scheme 1.1 (i) *LDA*, *EtI*; (ii) *LiAlH₄*; (iii) *acetone*, *H⁺*, 53% (over 3 steps); (iv) *O₃*, *Ph₃P*; (v) *Br₂*, *CH₃OH*, 78%; (vi) *NaH*, *PhCO₂Me*; (vii) *DBU*, *ArSO₂N₃*, 78% (over 2 steps); (viii) *Rh₂ Oct₄* (cat.), 89%; (ix) *LiAlH₄*; (x) *PhCH₂Br*, *NaH*, 75% (over 2 steps); (xi) *H⁺*, *H₂O*; (xii) *TsCl*, *py*, 66%.

procedure¹⁸ the epoxide was reduced to give the 2-hydroxycitronellol [10]. Following periodate cleavage¹⁹ and subsequent reductive workup norcitronellol [11] was formed. The unstable azide [12] was then prepared and subjected to ozonolysis followed by phosphonate condensation and reduction of the azide²⁰ with triphenyl phosphine to afford a 5.6:1 mixture of [13] and [14]. For the convergent assembly of [1], tosylate [8] was alkylated with piperidine [13] to give bicycle [15] [Scheme 1.3]. Activation of the secondary alcohol group by conversion into a brosylate followed by treatment with base



Scheme 1.2 (i) *t*-BuOOH, (*i*-PrO)₄Ti, (-)DET; (ii) NaBH₃CN, BF₃·OEt₂, 79% (over 2 steps); (iii) NaIO₄; (iv) NaBH₄, 61% (over 2 steps); (v) TsCl, py; (vi) NaN₃, 78% (over 2 steps); (vii) O₃, Ph₃P; (viii) EtO₂POCH₂CO₂Et; (ix) Ph₃P, H₂O, 68% (over 3 steps).



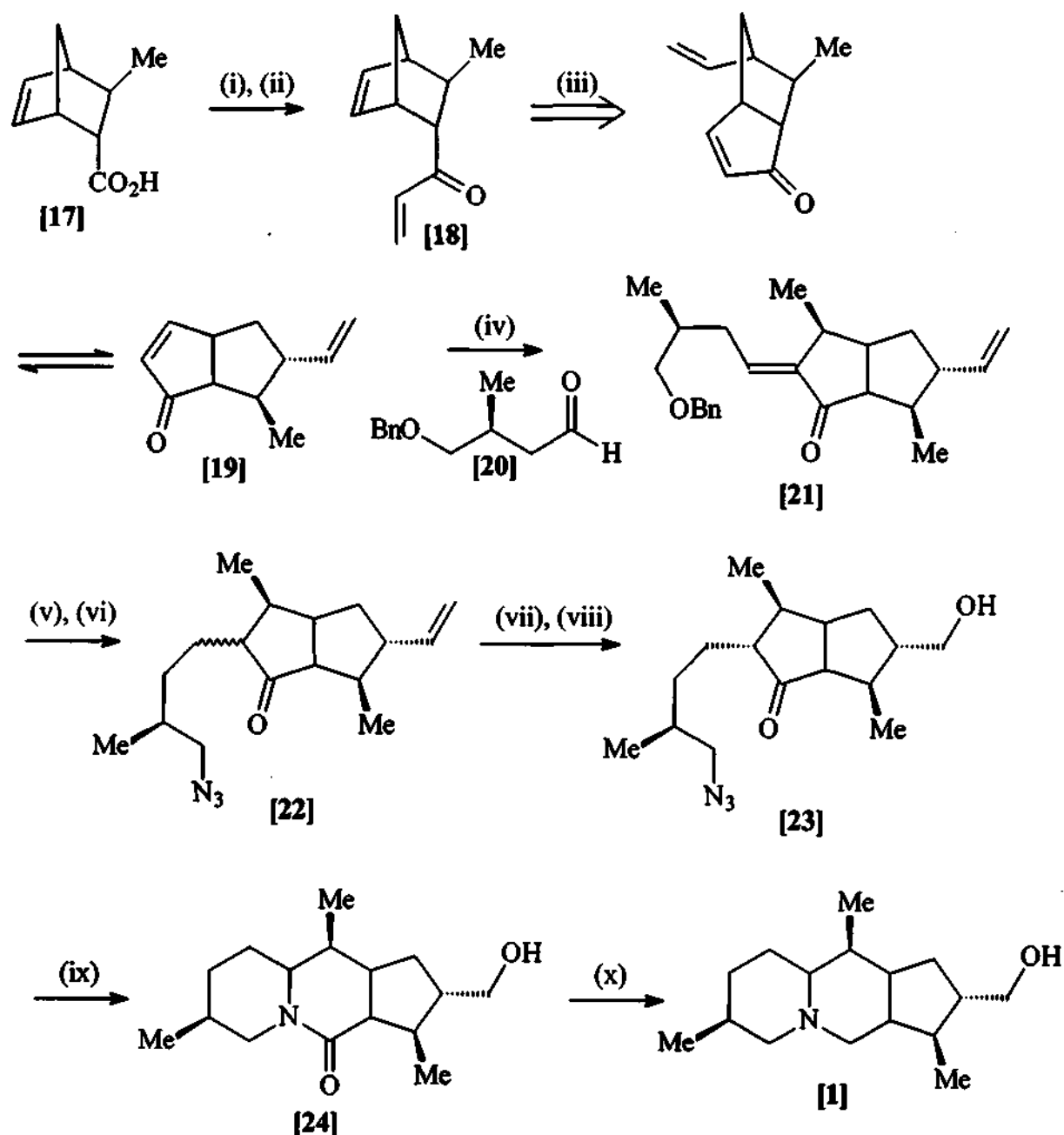
Scheme 1.3 (i) K₂CO₃, PhCH₃, Bu₄NI, Δ, 56%; (ii) BSCl, pyridine; (iii) LiHMDS, 53% (over 2 steps); (iv) LiAlH₄; (v) PhS₂, Bu₃P; (vi) Na, NH₃, 66% (over 3 steps).

allowed cyclisation to proceed smoothly to afford the cyclic ester [16]. Then ester [16] was reduced to the corresponding alcohol, which was then converted to the sulfide.²¹ Dissolving metal reduction²² was then used to effect desulfurization and debenzylolation to give [1].

The linear synthesis by Wroblewski, Sahasrabudhe and Aube¹⁴ features an intramolecular Schmidt reaction [Scheme 1.4].²³ The synthesis comprises 13 steps and has an overall yield of 5%. Firstly norbornene [17] was prepared using a second generation metathesis catalyst featuring a tandem ring-opening/ring-closing metathesis (ROM/RCM) reaction.²⁴ The conversion of acid [17] to the corresponding vinyl ketone [18] was carried out via the Weinreb amide.²⁵ Treatment of [18] with Grubb's catalyst afforded the bicyclic enone [19]. The enone [19] then underwent treatment with Me_2CuLi followed by quenching with aldehyde [20] to yield enone [21]. Compound [21] was treated with Na/NH_3 to effect both cleavage of the benzyl ether and reduction of the enone. Ozonolysis of [22] followed by DMS workup and careful reduction with NaBH_4 gave primary alcohol [23]. Treatment of [23] with TfOH resulted in an intramolecular Schmidt reaction forming lactam [24] as the sole enantiomer. The lactam [24] was then reduced to form [1] using LAH. Thanks to this synthetic route 100 mg of alkaloid 251F was prepared and was subsequently submitted for biological screening. To the best of our knowledge, the results of these biological tests have not yet been published.

The convergent synthesis utilized by Taber and You involved the preparation of alkaloid 251F in an overall number of 26 steps with an overall yield of 2.7%. The linear synthesis of Wroblewski, Sahasrabudhe and Aube comprises 13 steps and has an overall yield of 5%. Contrary to convention, the convergent approach was the lower yielding synthesis.

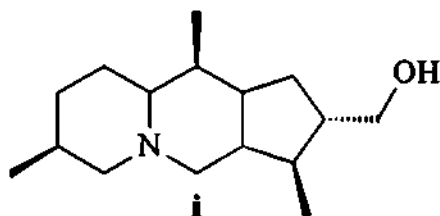
Generally, convergent syntheses are more efficient but in this case the linear synthesis proves to be the more efficient of the two syntheses.



Scheme 1.4 (i) $\text{HNMe(OMe)}\cdot\text{HCl}$, BOP, TEA; (ii) $\text{CH}_2=\text{CHMgBr}$, 85%; (iii) 5mol% Grubb's cat., ethylene, CH_2Cl_2 , 93%; (iv) Me_2CuLi then **[20]**, 65%; (v) Na, NH_3 ; (vi) $\text{Zn(N}_3)_2\cdot 2\text{ pyr}$, DEAD, PPh_3 , 50%; (vii) O_3 , DMS; (viii) NaBH_4 , 50% (over 2 steps) (4:1 $\alpha:\beta$); (ix) TjOH, 79%; (x) LAH, 86%.

ABSTRACT

Alkaloid, 251 F [i] has been isolated, by Daly *et al.*, from the skin extracts of two populations of the dendrobatid frog *Minyobates bombetes*. However, neither the biological activity, nor the absolute stereochemistry of the alkaloid has been investigated due to



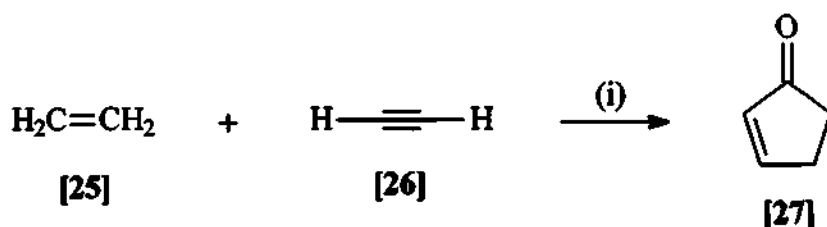
severe constraints on the availability of natural material. Hence the important need to devise synthetic methods to make more of this natural product.

Before embarking on such an ambitious task it was decided to perform a set of model studies to probe the feasibility of employing the Pauson-Khand reaction to construct the cyclopentane ring of alkaloid 251F. For the model studies 5-membered ring precursors were used to show the generality of the methodology so that a number of tricyclic systems would be accessible using the same methodology. Our work also serves to extend the scope of the Pauson-Khand reaction to include propargylated-lactams and thiolactams.

During model studies of the Pauson-Khand reaction it was found that the thiolactam gave consistently higher yields than the lactam. After further investigation it seemed probable that the sulfur atom of the thiocarbonyl is positioned at a distance which favours coordination to the cobalt atom. This in turn would help stabilize the intermediate complex and thus increase the yield of the reaction.

1.3 Introduction to the Pauson-Khand Reaction

The Pauson-Khand reaction is an efficient tool for the rapid assembly of cyclopentenone rings [27]. The reaction involves the co-cycloaddition of an alkyne [26], an alkene [25] and carbon monoxide, mediated by a transition metal carbonyl complex, usually $\text{Co}_2(\text{CO})_8$ [Scheme 1.5].²⁶ Yields are often improved by the use of promoters such as

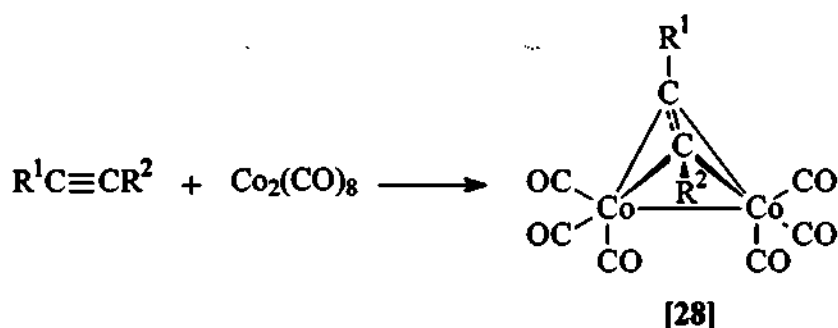


Scheme 1.5 (i) carbon monoxide

N-methylmorpholine *N*-oxide (NMO). The cyclopentenone products are very useful building blocks thanks to their ambident electro- and nucleophilicity which provide ample opportunity for the creation of additional carbon-carbon bonds. The overall process is a three-component [2 + 2 + 1] cycloaddition reaction, which incorporates the alkene π -bond, an alkyne π -bond and the carbon atom of carbon monoxide into the new five-membered ring.²⁶ The reaction displays significant degrees of regio- and stereochemical selectivity.²⁶ The reaction has taken its place as an important methodological approach to the cyclopentenone system, which is a focus for continued development by research groups, and has been utilised extensively in synthetic applications.²⁶

1.3.1 Pioneering Work by Pauson and Khand

The discovery of this reaction arose from the postulate that alkenes might insert into the hexacarbonyldicobalt alkyne complexes [28] [Scheme 1.6].²⁷



Scheme 1.6

Initially the study involved the use of strained alkenes.²⁷ The typical reaction involved heating a mixture of the alkene and the hexacarbonyldicobalt alkyne complex [28] in a hydrocarbon or ethereal solvent.²⁸ Early studies established that reasonable synthetic yields in the 30-60% range, and significant regio- and stereoselectivity could be expected.²⁸ The reaction appeared to involve alkene insertion but the intermediate complexes arising from this insertion could not be isolated.²⁷ The reaction alters behaviour when alkenes bearing strong electron withdrawing substituents are used. In fact, this is the main limitation of the cyclopentenone-forming reaction.²⁷ Thus alkenes bearing electron-withdrawing groups such as CN, CO₂R, SO₂R, etc. yield conjugated dienes instead [Scheme 1.7].²⁷ Unfortunately, this mode of reaction has not given sufficiently good yields to be an attractive synthetic route.²⁷



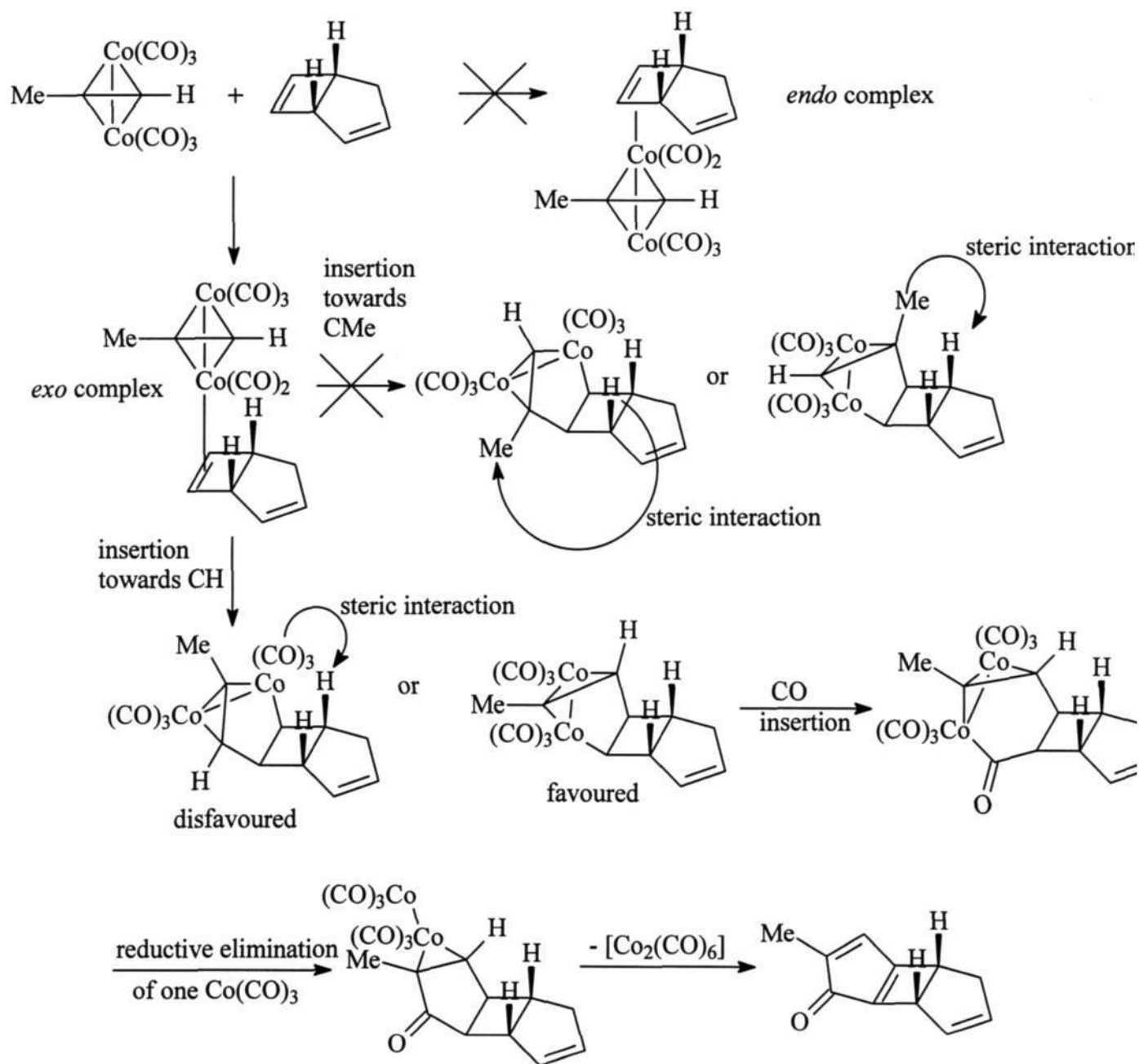
Scheme 1.7 Z=CN, CO₂R, SO₂R etc.

The scope of the Pauson-Khand reaction has been extended to intra- and intermolecular cyclopentenone formation. Various transition metals have been used to facilitate the Pauson-Khand reaction, such as Ti, Ru, Rh and even Ir.²⁹ The conditions of the reaction

now include the use of microwave irradiation³⁰ and ionic liquids.³¹ These advances, along with the introduction of promoters, have made the Pauson-Khand reaction a powerful synthetic tool.

1.3.2 Mechanism

Any direct studies of the mechanism have been limited to the intermediate alkyne complex [28].²⁸ All attempts to observe intermediates spectroscopically beyond the alkyne complexation stage have been unsuccessful, with the only species observed being the final products themselves.²⁸ Thus, it would appear that the rate-determining step, that follows complexation, occurs early in the mechanistic sequence and prevents the build-up of any subsequent intermediates to detectable levels.²⁸ However, even with the lack of direct mechanistic evidence, a hypothesis has been inferred from regio- and stereochemical observations in a large number of examples.²⁸ The principal interactions that control the mechanistic pathway appear to be steric in nature.²⁸ Complexation of the alkene takes place *via* a standard dissociative mechanism, which is possibly reversible [Scheme1.8].²⁸ The less hindered *exo* face of the alkene's π -bond preferentially complexes to the metal.²⁸ In the next step, insertion of the complexed face of the alkene π -bond into one of the formal cobalt-carbon bonds of the alkyne complex takes place. This is thought to be both the rate- and product-determining step and is an irreversible insertion.²⁸ During this insertion into the cobalt-carbon bond, regiochemistry with respect to the alkyne and alkene is determined.²⁸ Insertion always takes place to minimize steric interactions. Once the new carbon-carbon bond with the alkyne carbon has been formed, carbon monoxide insertion takes place.²⁸ Then reductive elimination of one cobalt moiety takes place followed by decomplexation of the other to give the final cyclopentenone product.²⁸

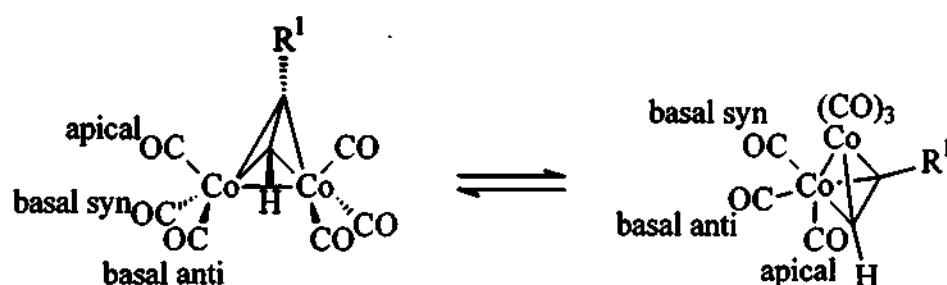


Scheme 1.8 Proposed mechanism of the Pauson-Khand reaction

1.3.3 Use of Tertiary N-oxide Promoters

In 1990 **Shambayati, Crowe and Shreiber**³² reported a new efficient method for executing the Pauson-Khand reaction under milder conditions with greater

stereoselectivity. They found that tertiary amine oxides readily promote intramolecular Pauson-Khand cyclisations at room temperature under an inert atmosphere of nitrogen or argon.³² It appeared that the *N*-oxide promoter is involved in the initial oxidation of a cobalt CO ligand to CO₂ by donation of the oxygen atom bonded to nitrogen. This would then provide an empty site for coordination of the olefin.³² Shen, Gao, Shi and Basolo, showed that the rate of oxygen atom transfer reactions to metal carbonyls were greatly increased in the presence of (CH₃)₃NO.³³ Following up on these results Jeong and co-workers³⁴ discovered that trimethylamine *N*-oxide (TMANO) dramatically increased the rate of the Pauson-Khand reaction. *N*-methylmorpholine *N*-oxide (NMO) was also very effective.³⁴ Under thermal conditions it is assumed that the alkyne complex undergoes decarbonylation at the *basal* carbon monoxide, which is *anti* relative to R¹ [Scheme 1.9].³⁵ This is then followed by coordination of the alkene to the complex. Since this is generally

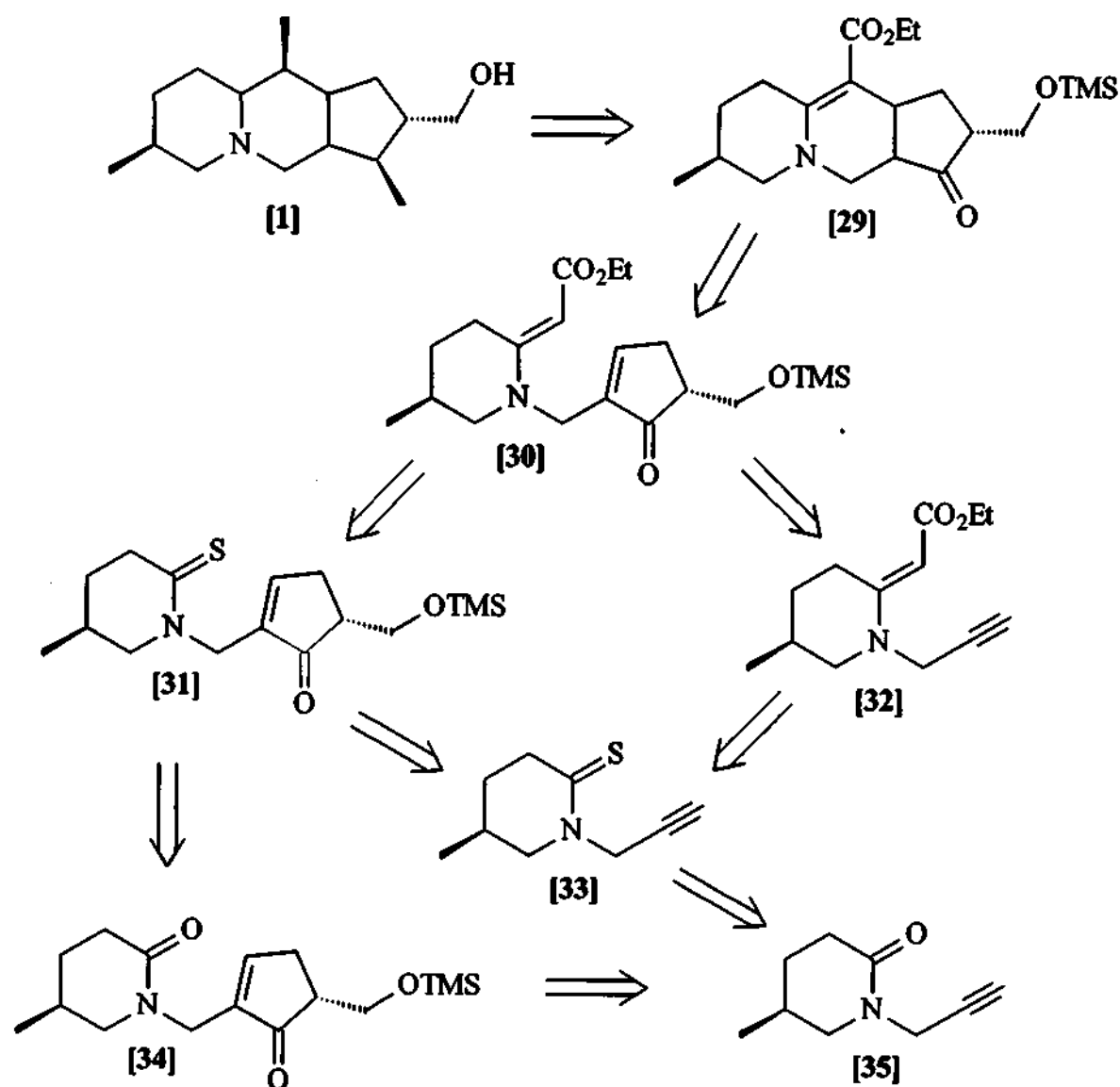


Scheme 1.9

accepted to be the rate -determining step, one can clearly see that by liberating a CO from the alkyne complex, the promoter has a significant impact on the yield and rate of the reaction.³⁵ The reason why such large quantities of a promoter, generally 3-6 equivalents, are needed is still unclear. Perhaps more efficient promoters will see these requirements decrease and lead to further improvements in the efficiency for the Pauson-Khand reaction.

1.4 Aims of the Investigation

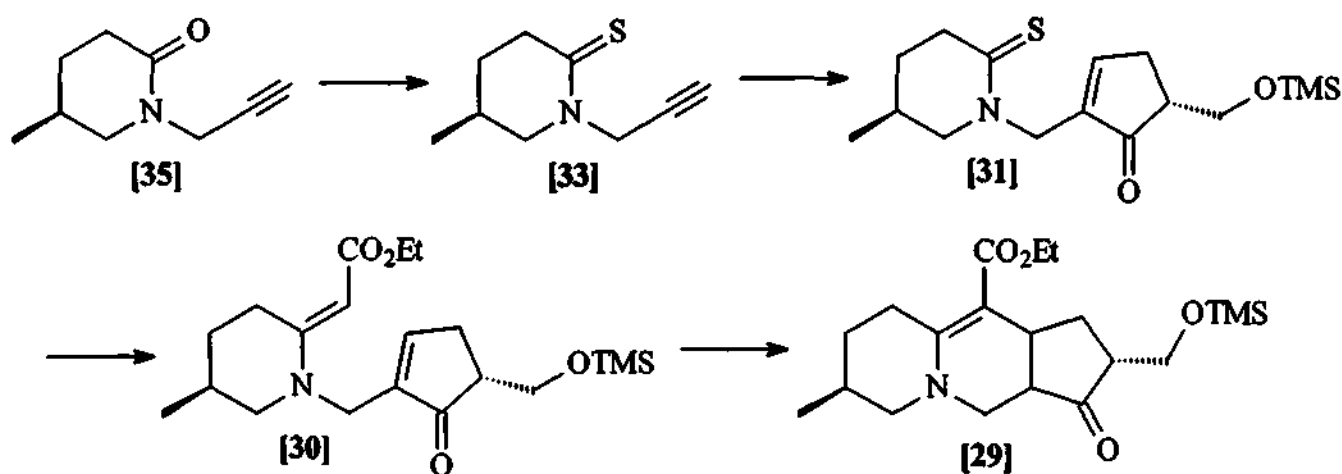
We wish to develop methodology that will allow us to synthesise alkaloid 251F. A key reaction in this approach is the Pauson-Khand reaction ($[33] \rightarrow [31]$ and $[32] \rightarrow [30]$) as shown in the retrosynthetic analysis below [Scheme 1.10]. Another important feature is the



Scheme 1.10 Retrosynthetic analysis of alkaloid 251F

flexibility of the approach. There are three possible synthetic routes that can be exploited to synthesise compound [30]. Each of these routes will be outlined in turn.

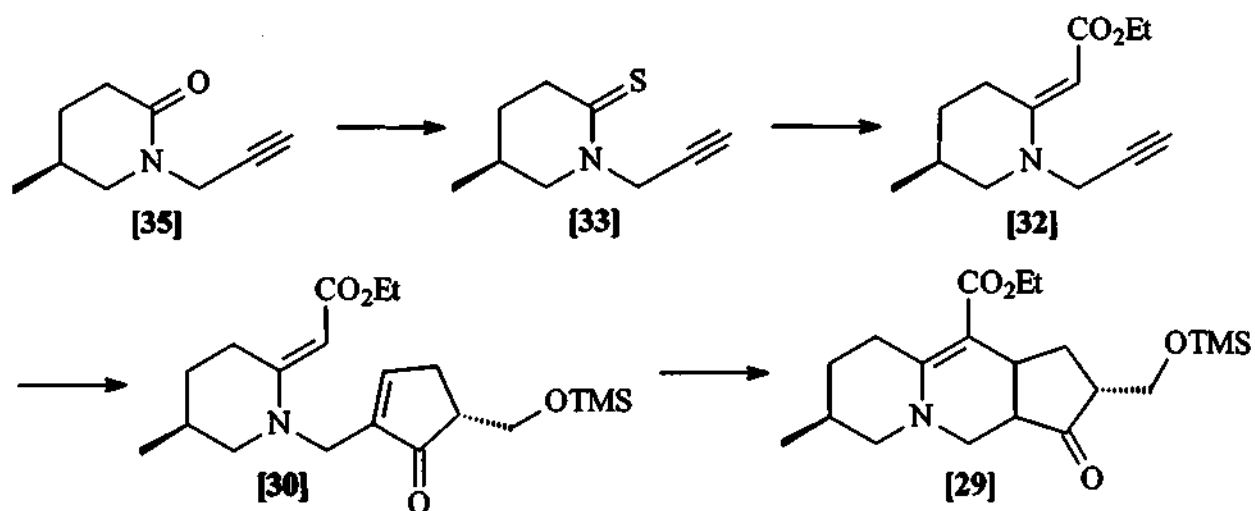
The first route that can be utilised in **Scheme 1.10** explores the possibility of performing a thionation reaction on lactam [35] [**Scheme 1.11**]. The Pauson-Khand thiolactam products [31] will be alkylated with ethyl bromoacetate by means of an Eschenmoser sulphide



Scheme 1.11 First proposed route to synthesis of alkaloid 251F.

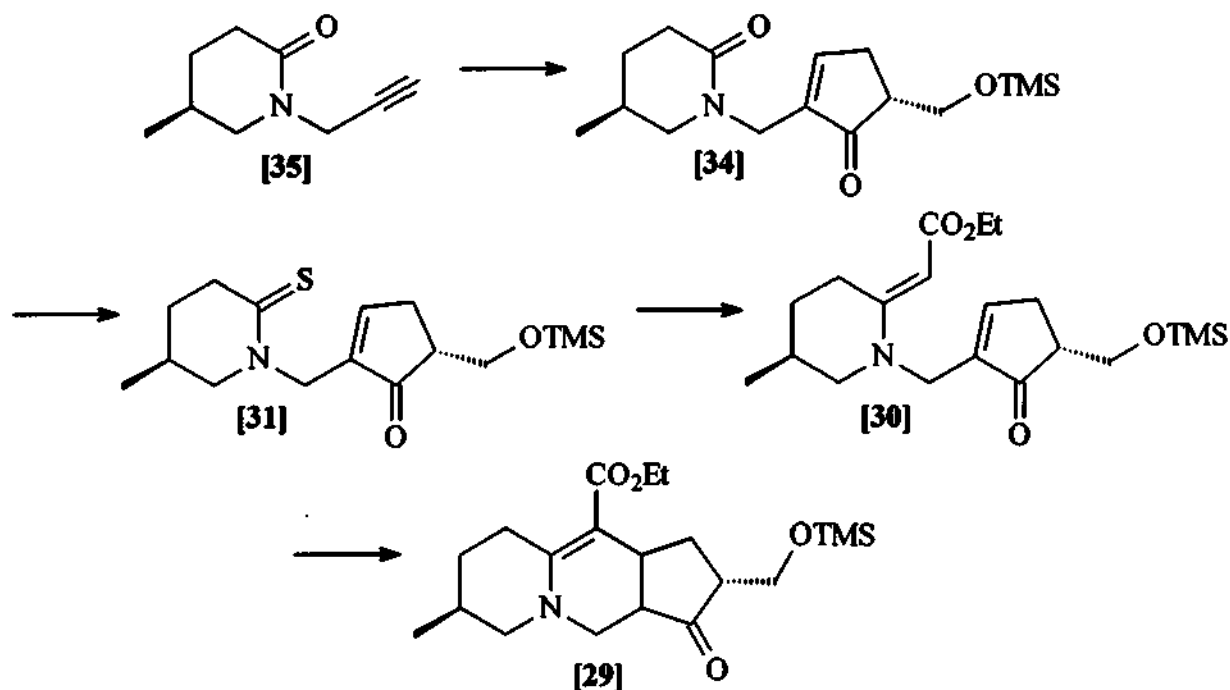
contraction reaction³⁶ in order to create the vinylogous urethane functional group [30]. It is hoped that the vinylogous urethanes will cyclise *in situ* to give the tricyclic ring system [29] analogous to that of alkaloid 251F.

The second approach, proposed in **Scheme 1.10**, involves first forming the *N*-propargylated vinylogous urethanes [32] and then using them as the alkyne in the Pauson-Khand reaction ([32] → [30]) [**Scheme 1.12**]. Once again it is hoped that a spontaneous cyclisation reaction ([30] → [29]) will take place, thereby creating the internal six-membered ring analogous to that of alkaloid 251F.



Scheme 1.12 *Second proposed route to the synthesis of alkaloid 251F.*

A third option presented in Scheme 1.10 is the possibility of performing the Pauson-Khand reaction ([35] \rightarrow [34]) on the lactam [Scheme 1.13]. If possible this intermediate would be chemoselectively thionated [31] and an Eschenmoser sulfide contraction executed to obtain the desired vinylogous urethane [30]. Hopefully, a spontaneous cyclisation would then occur to assemble the tricyclic ring system [29] which is found in alkaloid 251F.

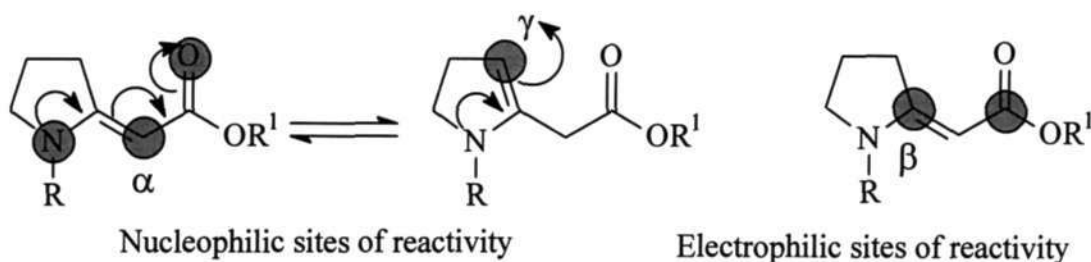


Scheme 1.13 *Third proposed route to the synthesis of alkaloid 251F.*

It should now be clear why the synthetic pathway illustrated **Scheme 1.10** is so flexible and as such provides a number of alternative routes to the target molecule that can be explored. Thus, if one route proves to be unsuccessful or inefficient we can pursue alternative approaches.

The next important feature is that of the use of vinylogous urethanes as pivotal intermediates. They are introduced by means of the Eschenmoser sulfide contraction ([33] \rightarrow [32] and [31] \rightarrow [30]). This reaction neatly introduces the two-carbon fragment necessary for the synthesis of alkaloid 251F with the ester carbonyl carbon destined to become the methyl group α to the bridgehead position. The nucleophilic enamine-like chemical reactivity of vinylogous urethanes as explained in the next paragraph is especially attractive in our synthesis.

Vinylogous urethanes are compounds in which a nitrogen atom is conjugated via a carbon-carbon double bond to an ester group. These compounds are thus β -acylated enamines. Vinylogous urethanes are so versatile as synthetic intermediates because they possess both nucleophilic and electrophilic properties [**Scheme 1.14**]. They are in principle able to react with electrophiles either at the nitrogen or the enamine carbon atom. Extended

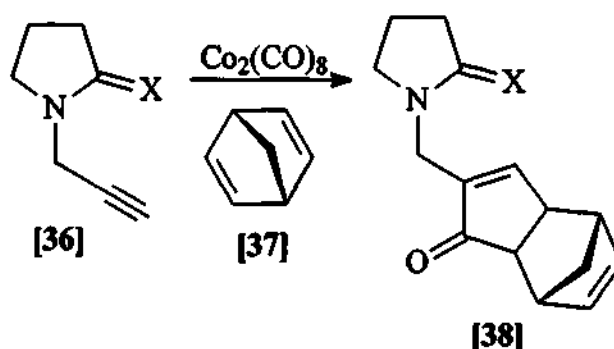


Scheme 1.14

tautomerism also renders the oxygen and the γ -carbon competitive nucleophilic sites. Additionally, the carbonyl carbon and the carbon atom β to the carbonyl carbon show electrophilic properties when reacting with appropriate nucleophiles³⁷ [Scheme 1.14].

Before embarking on such an ambitious task we decided to perform a set of model studies to probe the feasibility of using the Pauson-Khand reaction to construct the cyclopentane ring of alkaloid 251F [Scheme 1.10]. For the model studies we thought we would include both 5- and 6-membered ring examples to show the generality of the methodology so that a number of tricyclic systems would be accessible using the same methodology.

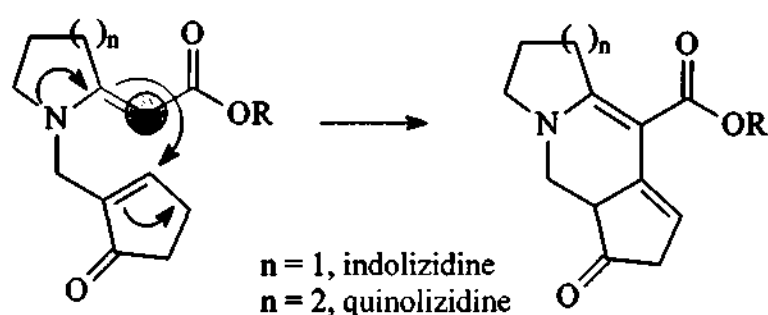
Our work also serves to extend the scope of the Pauson-Khand reaction to include propargylated-lactams and thiolactams [Scheme 1.15]. To the best of our knowledge these



Scheme 1.15 $X=O$ or S

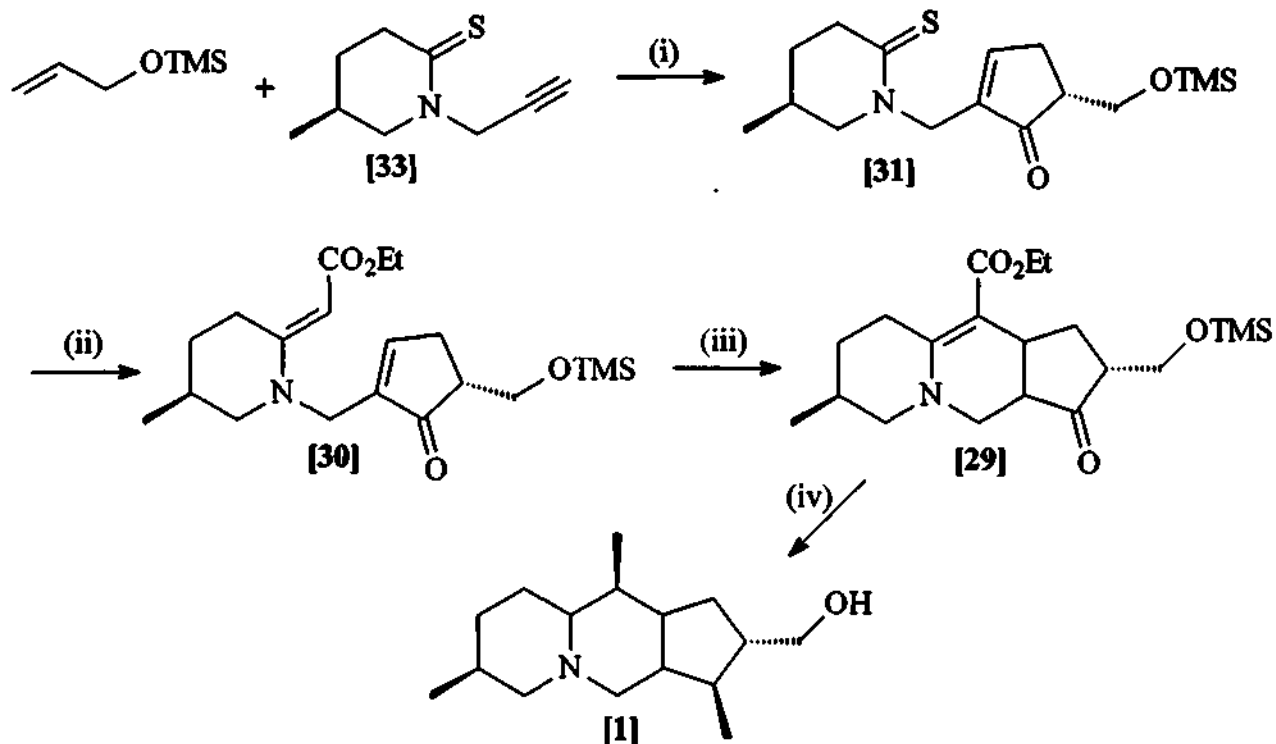
systems have not been studied before. The Pauson-Khand reaction generally gives better yields when strained cyclic alkenes are used.²⁹ Thus, although not directly useful for the synthesis of alkaloid 251F, norbornadiene [37], being a strained cyclic alkene, was chosen as a model alkene for the methodological study with the propargylated lactams and thiolactams.

The appropriate Pauson-Khand products [38] would then be converted into vinylogous urethanes and cyclisation attempted. More specifically, in our case the enamine moiety of the vinylogous urethane would do a conjugate addition to the enone to close the six-membered ring [Scheme 1.16].³⁸ The synthetic versatility of vinylogous urethanes have been extensively explored by Michael J. *et al*, who has made a considerable contribution in this area.³⁸ The enone functionality would have been conveniently formed by the Pauson-Khand reaction. It is hoped that this cyclisation can be achieved by simply heating the vinylogous urethane in the appropriate solvent.



Scheme 1.16

Looked at in terms of a possible total synthesis of alkaloid 251F the most appropriate alkene to use would be allyl alcohol. The effect of protecting the alcohol (e.g. as its TMS ether [Scheme 1.17]) will be investigated to see how yields and the regio- and stereoselectivity of the reaction are influenced. The exact synthetic route used to obtain the vinylogous urethane [30] can vary, but once this product is obtained cyclisation will be attempted. Upon extended heating ring closure should take place to form a tricyclic compound [29]. This synthesis would be expeditious allowing the construction of the tricyclic skeleton of alkaloid 251F in only 4 steps! Once this tricyclic compound has been obtained the TMS protecting group can be removed, and the enaminone double bond reduced using sodium cyanoborohydride. Thereafter, the ester functionality will be reduced



Scheme 1.17 (i) Pauson-Khand reaction; (ii) Eschenmoser coupling; (iii) Cyclisation; (iv) Deprotection, introduction of the final methyl group using MeMgBr or MeLi, Functional Group Interconversion.

to the required methyl group and an appropriate Grignard reagent reacted with the ketone to introduce the missing methyl group. A final removal of the tertiary alcohol would complete the synthesis of alkaloid 251F. The stereoselectivity of all the above reactions, especially the cyclisation reaction, can be investigated by analysing the ratio of diastereomeric products.

The following chapter will give an account of the successes and failures incurred when investigating the methodology that would be most successful for performing the Pauson-Khand reaction. It is potentially the lowest yielding reaction in this proposed synthesis and therefore limiting to the overall yield. This is clearly a crucial reaction in allowing us to

synthesise the skeleton of alkaloid 251F. In subsequent chapters I will describe how the synthetic route detailed above was adapted to overcome a number of synthetic challenges.

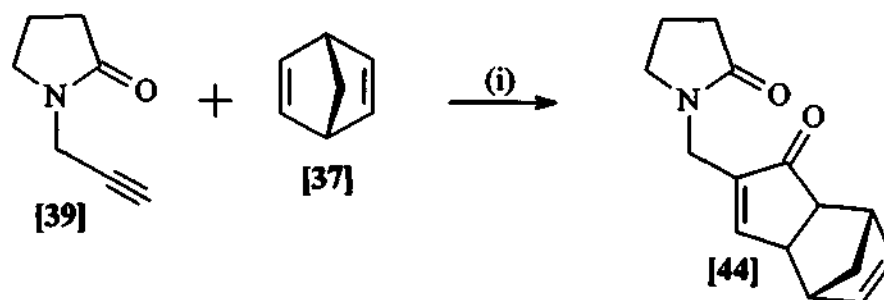
CHAPTER 2

MODEL STUDIES

The previous chapter laid the foundation for this project. This chapter will discuss the experimental results obtained for model studies of the Pauson-Khand reaction between propargylated thiolactams and various alkenes which to the best of our knowledge had not been attempted. Two different alkynes [39] and [40] were reacted with a variety of alkenes. The first section will detail the formation of the Pauson-Khand products using 2(2-propynyl)tetrahydro-2*H*-pyrrol-2-one [39] as the alkyne. The reactions that will subsequently be discussed all involve the use of 1-(2-propynyl)tetrahydro-2*H*-pyrrole-2-thione [40] as the alkyne in the Pauson-Khand reaction. Both alkynes were reacted with a series of alkenes: norbornadiene [37], allyl alcohol [41], cyclohexene [42] and tetrahydro-2-(2-propenyloxy)pyran [43] respectively. The results of these reactions will be discussed along with the inclusion of selected carbon and proton NMR spectroscopic data of some of the compounds synthesized.

2.1 Pauson-Khand reactions of 2(2-propynyl)tetrahydro-2*H*-pyrrol-2-one [39] with various alkenes

2.1.1 Norbornadiene [37]



Scheme 2.1 (i) $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2 ; 42%.

2-(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39] was synthesized in the following manner. Pyrrolidin-2-one was dissolved in THF and then reacted with propargyl bromide using sodium hydride as a base.³⁹ Purification using radial chromatography afforded pure 2-(2-propynyl)tetrahydro-2H-pyrrol-2-one [39] as a yellow oil in 74% yield. Product identification was carried out using ^1H and ^{13}C NMR spectroscopy. The Pauson-Khand reaction was then performed using a standard procedure, adapted from the one reported by Jeong and co-workers.³⁴ Initially a cobalt-alkyne complex is formed by adding dicobalt octacarbonyl to the alkyne, in this case 2-(2-propynyl)tetrahydro-2H-pyrrol-2-one [39], dissolved in dichloromethane and stirring the resulting mixture at room temperature for half an hour. The reaction mixture is then cooled to 0°C , before the addition of the alkene followed by the promoter, *N*-methyl morpholine *N*-oxide (NMO). It is important to cool the reaction mixture because when the NMO is added the mixture bubbles vigorously, as CO is liberated, and the reagent tends to overflow at room temperature. The reaction mixture is then allowed to warm to ambient temperature and left to stir overnight. After filtration and purification using radial chromatography the desired product 1{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44] was obtained as white crystals in a 42% yield. This Pauson-Khand reaction was performed in various solvents. Dichloromethane proved to be the best; it gave better yields than THF (30%) and

acetonitrile (30%). Confirmation of the product was obtained from ^1H and ^{13}C NMR spectroscopic data, HRMS and crystallographic data.

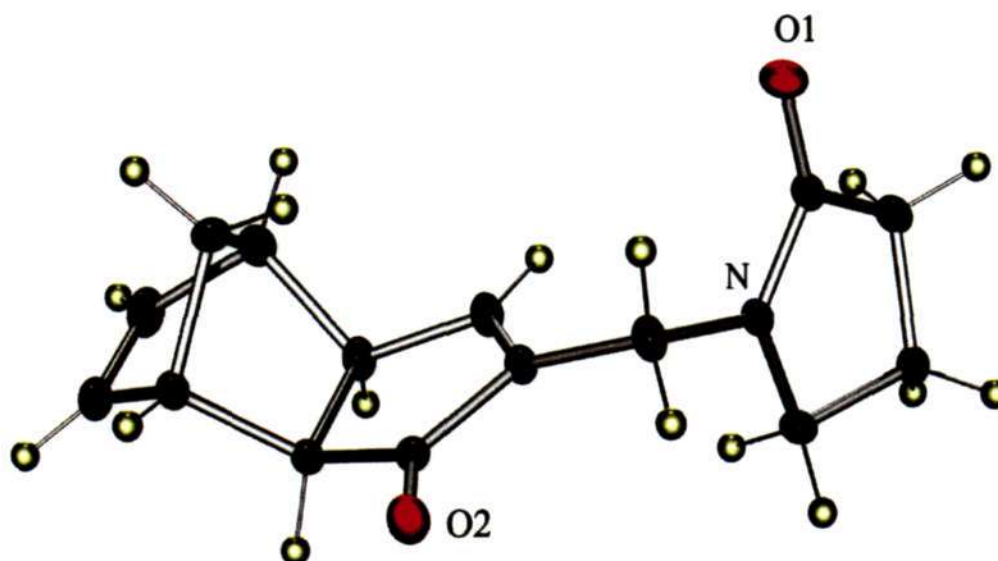


Figure 2.1 The X-ray crystal structure of 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44]

Figure 2.1 shows the crystal structure of 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone while Figure 2.2 shows the carbon NMR spectrum for the same compound. From the X-ray crystal structure it was found that the crystal system was monoclinic and the space group was $P2_1/n$. The total number of molecules per unit cell (Z) was four with one molecule per asymmetric unit. Only the *exo*-product was formed – Pauson-Khand reactions typically disfavour formation of the *endo*-product. In addition it can be seen that in all molecules the lactam substituent is attached to the position alpha to the carbonyl group of the cyclopentenone ring. The formation of the cyclopentenone ring is

confirmed by both NMR and X-ray data, thereby showing that the Pauson-Khand reaction was successfully carried out. In Figure 2.2 shows the ^{13}C NMR spectrum of 1{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44]. Obviously the significant changes occur at the alkyne bond of the starting material. The terminal alkyne carbon resonates at 78.5 ppm, the other alkyne carbon gives rise to a signal at 71.4 ppm. Figure 2.2 clearly shows that these signals are absent in the product. A new carbonyl signal (C_1) now appears at 208 ppm. The DEPT NMR experiment indicates that the signal at 162 ppm is due to a CH group. GHMQC spectroscopic data (Figure 2.3) shows a correlation to C_1 . Thus, the signal at 162 ppm was assigned as the vinyl carbon C_3 . This carbon was the terminal alkyne carbon of the starting material. The signal observed at 145 ppm proved to be a quaternary carbon by DEPT NMR evidence. The GHMQC spectroscopic data showed a correlation to C_3 . Accordingly, the signal at 145 ppm was assigned as C_4 .

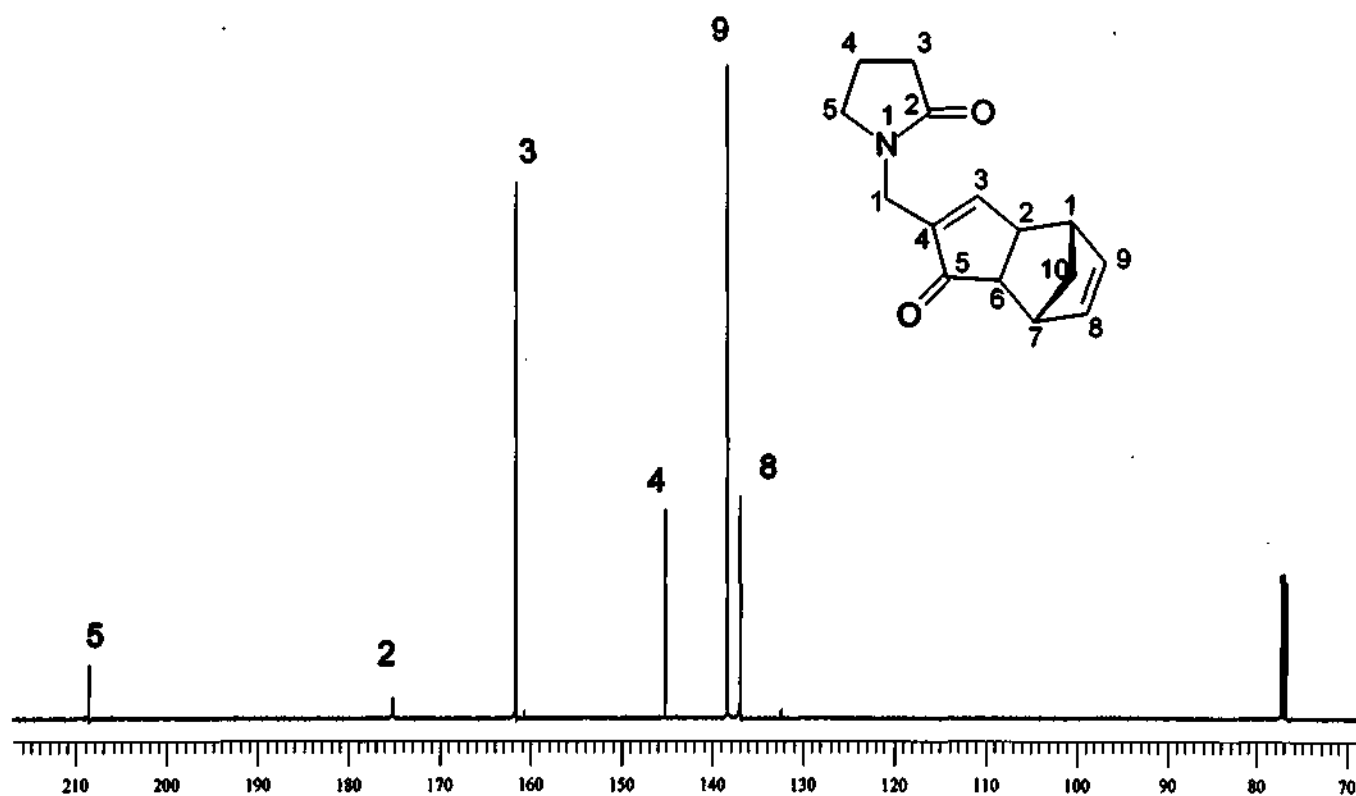
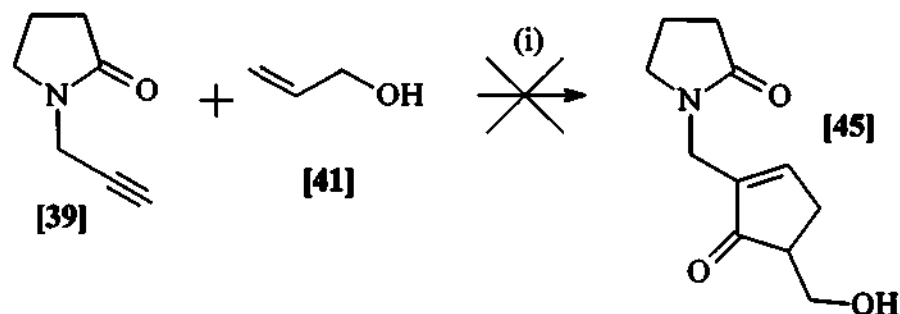


Figure 2.2 ^{13}C NMR spectrum of 1{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44] in CDCl_3

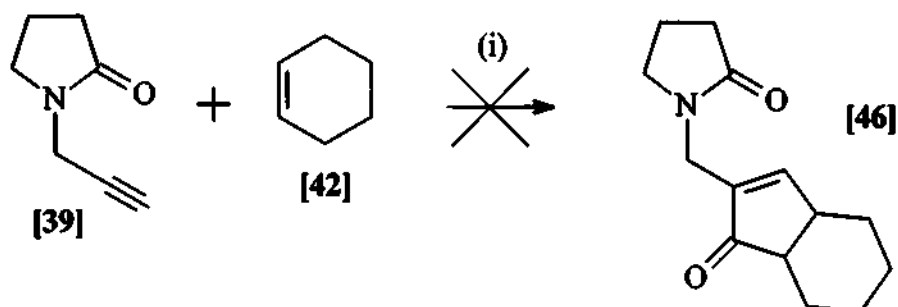
2.1.2 Allyl alcohol [41]



Scheme 2.2 (i) $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2

Allyl alcohol [41] was obtained from commercial sources and reacted with 2(2-propynyl)tetrahydro-2H-pyrrol-2-one [39] and dicobalt octacarbonyl in CH_2Cl_2 and promoted using NMO. Disappointingly, none of the desired product was obtained. Unreacted starting materials were recovered.

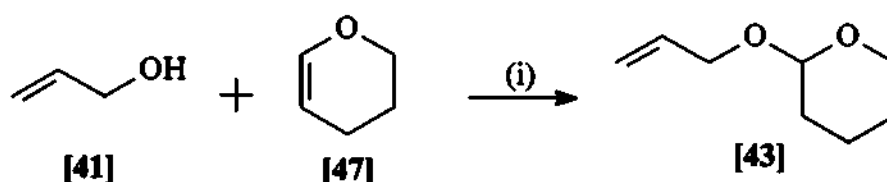
2.1.3 Cyclohexene [42]



Scheme 2.3 (i) $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2

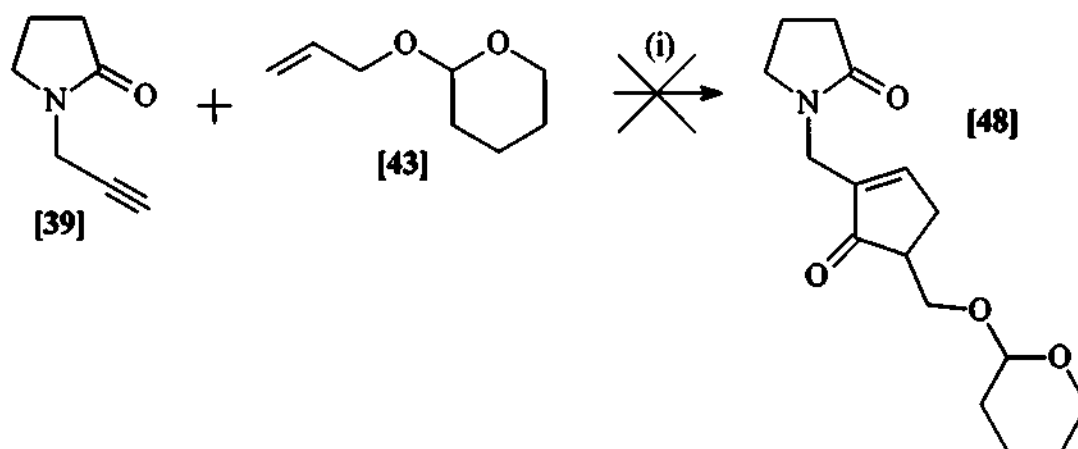
2(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39] was added to dicobalt octacarbonyl in dichloromethane to form the corresponding complex. This complex was then reacted with cyclohexene [42] in the presence of NMO as promoter. However, none of the desired product was obtained. Starting materials were recovered.

2.1.4 Tetrahydro-2-(2-propenyloxy)pyran [43]



Scheme 2.4 (i) *p*-Toluene-sulfonic acid, CH₂Cl₂; 70%.

Tetrahydro-2-(2-propenyloxy)pyran [43] was formed by reacting allyl alcohol [41] with dihydropyran [47] and a catalytic amount of *p*-toluene-sulfonic acid in CH₂Cl₂ [Scheme 2.4].⁴⁰ The product was distilled under a vacuum of 10mmHg at 80-83°C. This compares with the literature value of 65-67°C at 20 torr.⁴⁰ The product was a colourless oil in a 70% yield and was unambiguously characterized by ¹H and ¹³C NMR spectroscopy.

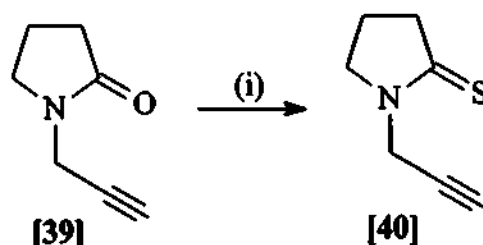


Scheme 2.5 (i) Co₂(CO)₈, NMO, CH₂Cl₂

Tetrahydro-2-(2-propenyloxy)pyran [43] was then reacted with the complex formed between cobalt octacarbonyl and 2(2-propynyl)tetrahydro-2H-pyrrol-2-one [39]. Unfortunately, none of the desired Pauson-Khand product [48] was obtained. Starting materials were recovered.

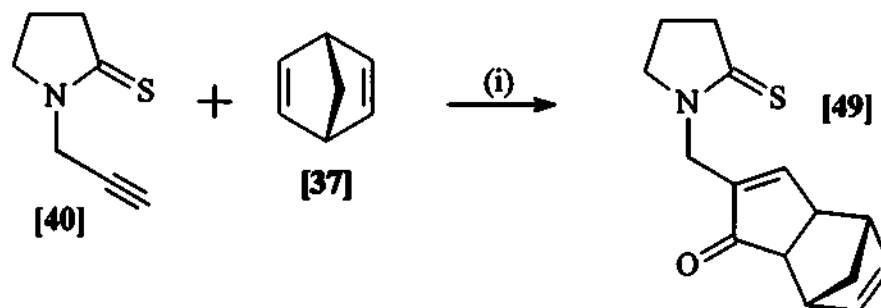
2.2 Pauson-Khand reactions of 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [40] with various alkenes

2.2.1 Norbornadiene [37]



Scheme 2.6 (i) P_4S_{10} , Na_2CO_3 , THF; 65%.

1-(2-Propynyl)tetrahydro-2H-pyrrole-2-thione [40] was synthesized by thionation of the corresponding lactam using Brillouin's method.³⁹ Thus phosphorus pentasulfide and sodium carbonate were mixed in THF to form a soluble sodium salt with the concomitant release of carbon dioxide. The salt was then reacted with 2-(2-propynyl) tetrahydro-2H-pyrrol-2-one [39] [Scheme 2.6]. After aqueous workup, purification using radial chromatography afforded 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione as a yellow oil in a 65% yield. Its structure was confirmed by ¹H and ¹³C NMR spectroscopy. The thiolactam [40] is unstable and tends to decompose under normal conditions. Thus 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [40] was stored under N₂ in a freezer.



Scheme 2.7 (i) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; 62%.

1-(2-Propynyl)tetrahydro-2*H*-pyrrole-2-thione [40] was subsequently reacted with norbornadiene [37] under the standard Pauson-Khand reaction conditions already described [Scheme2.7]. After purification using radial chromatography the desired product was obtained as white crystals [49] in 62% yield. Its structure was confirmed by ^1H and ^{13}C NMR spectroscopy, as well as GC-MS and solution of the crystal structure.

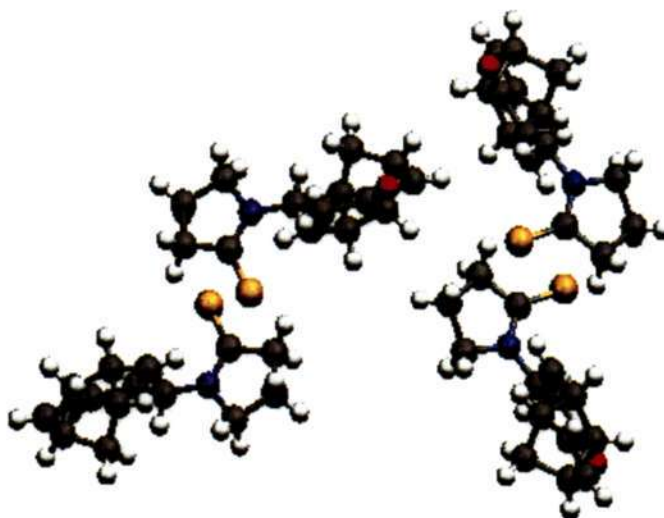


Figure 2.4 *X-ray crystal structure of enantiomer (1R,7S)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one and of enantiomer (1S,7R)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [49] unit cell*

There are a number of interesting details, which the crystal structure revealed. The most noticeable feature is that there are four molecules present in each asymmetric unit. There is also a prominent contrast with the crystal structure of 1 {[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone because two enantiomers are present in each asymmetric unit. The crystal has therefore formed as a racemate, which is unusual. This is

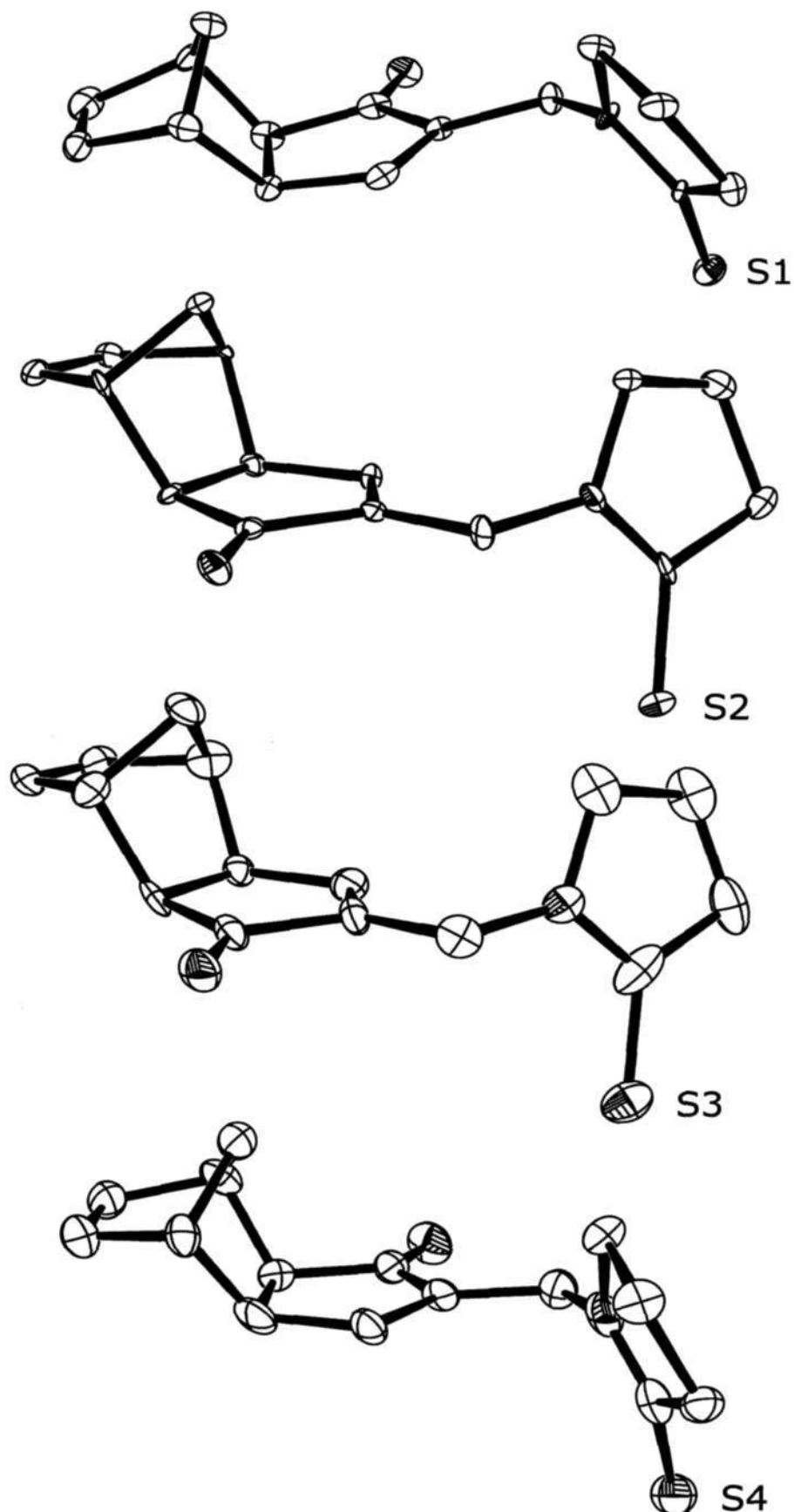


Figure 2.5 X-ray crystal structure of enantiomer (*1R,7S*)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one and enantiomer (*1S,7R*)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [49]

difficult to see because of the puckering and twisting of the molecules in the unit cell. Figure 2.5 offers a clearer view. The four molecules in the unit cell have been aligned and stacked on top of each other. From the X-ray crystal structure it was found that the crystal system was orthorhombic and the space group was $Pb21a$. Since the orthorhombic crystal system possesses four asymmetric units the total number of molecules per unit cell (Z) was sixteen, with four molecules per asymmetric unit. Each molecule in the unit cell is the *exo*-product, as was expected since the Pauson-Khand reaction typically disfavours the formation of the *endo*-product. Additionally it can be seen that in all cases the thiolactam substituent is attached to the position alpha to the carbonyl group of the cyclopentenone ring. Molecules S1 and S4 are identical stereoisomers – the $1S/7R$ isomer. Similarly molecules S2 and S3 are conformational isomers of one another while being enantiomers of molecules S1 and S4 respectively.

The enantiomers are illustrated below [Figure 2.6].

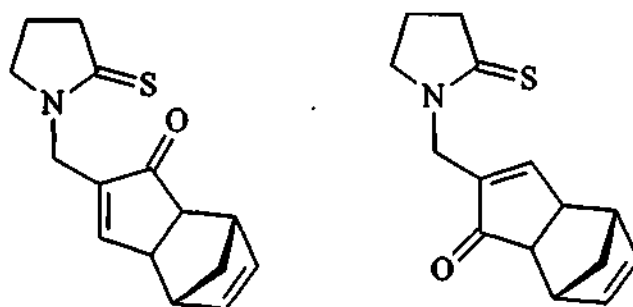


Figure 2.6 ($1S,7R$)-4-[(thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}] deca-3-one (left) and ($1R,7S$)-4-[(thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}] deca-3-one (right)

The successful formation of the cyclopentenone ring is also corroborated by the NMR data. The ^{13}C NMR spectrum bears witness to the cyclopentenone ring very clearly. In Figure 2.7 the quaternary carbon (C_4) of the cyclopentenone ring is observed at 143 ppm and the

vinyl carbon (C_3) at 164 ppm. The carbonyl signal (C_5) resonates at 209 ppm while the thiocarbonyl produces a characteristic signal at 201 ppm and is easily distinguished from the lactam carbonyl (175 ppm) in Figure 2.2. HRMS results yielded a mass of 259.1023, which is in good agreement with the calculated mass of 259.1031 a.m.u.

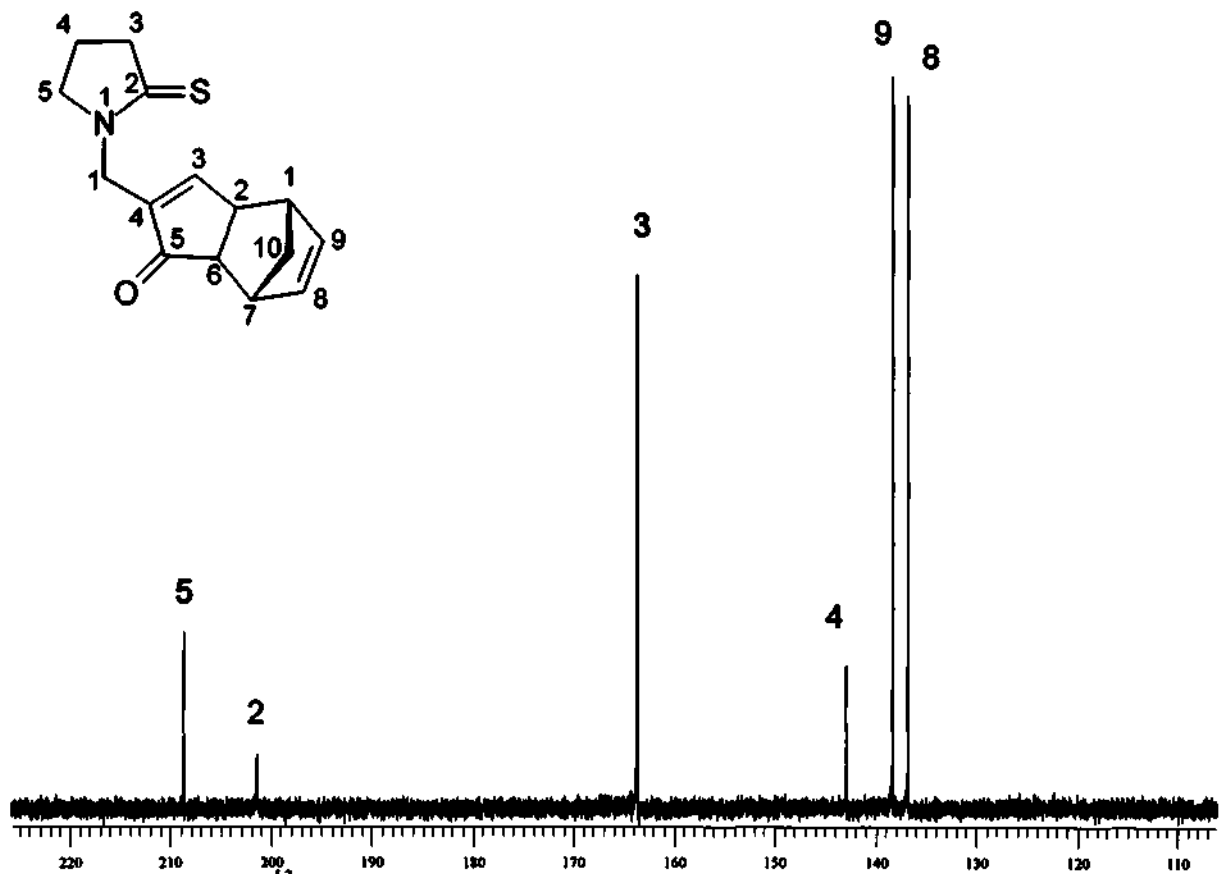
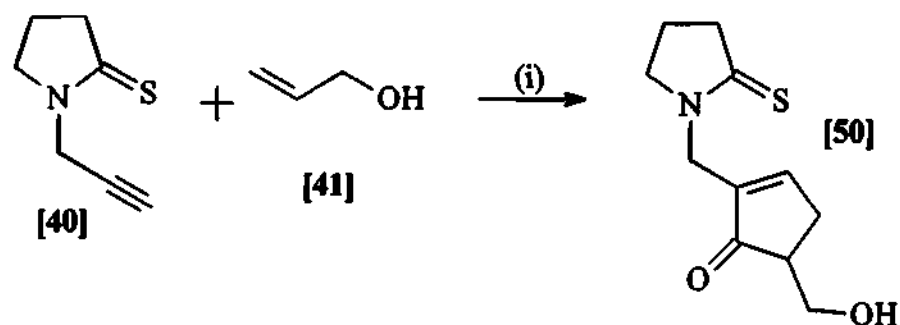


Figure 2.7 ^{13}C NMR spectrum of (1*R/S*,7*S/R*)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [49] in CDCl_3

2.2.2 Allyl alcohol [41]



Scheme 2.8 (i) $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2 ; 10%.

1-(2-Propynyl)tetrahydro-2*H*-pyrrole-2-thione was dissolved in CH₂Cl₂ and Co₂(CO)₈ added to form a complex with the alkyne. Allyl alcohol and NMO were then introduced to complete the reaction. 5-(Hydroxymethyl)-2-[(2-thioxo-1-pyrrolidinyl)methyl]-2-cyclopenten-1-one [50] was obtained in a 10% yield as a yellow oil. This was confirmed by the ¹H and ¹³C NMR spectra obtained for the product.

Once again, the significant changes occur at the alkyne bond of the starting material. The terminal alkyne carbon resonates at 78.5 ppm, while the other alkyne carbon gives rise to a signal at 71.4 ppm. Figure 2.2 shows that these signals are clearly absent in the product. A complete description of how the new signals were assigned will not be detailed to avoid

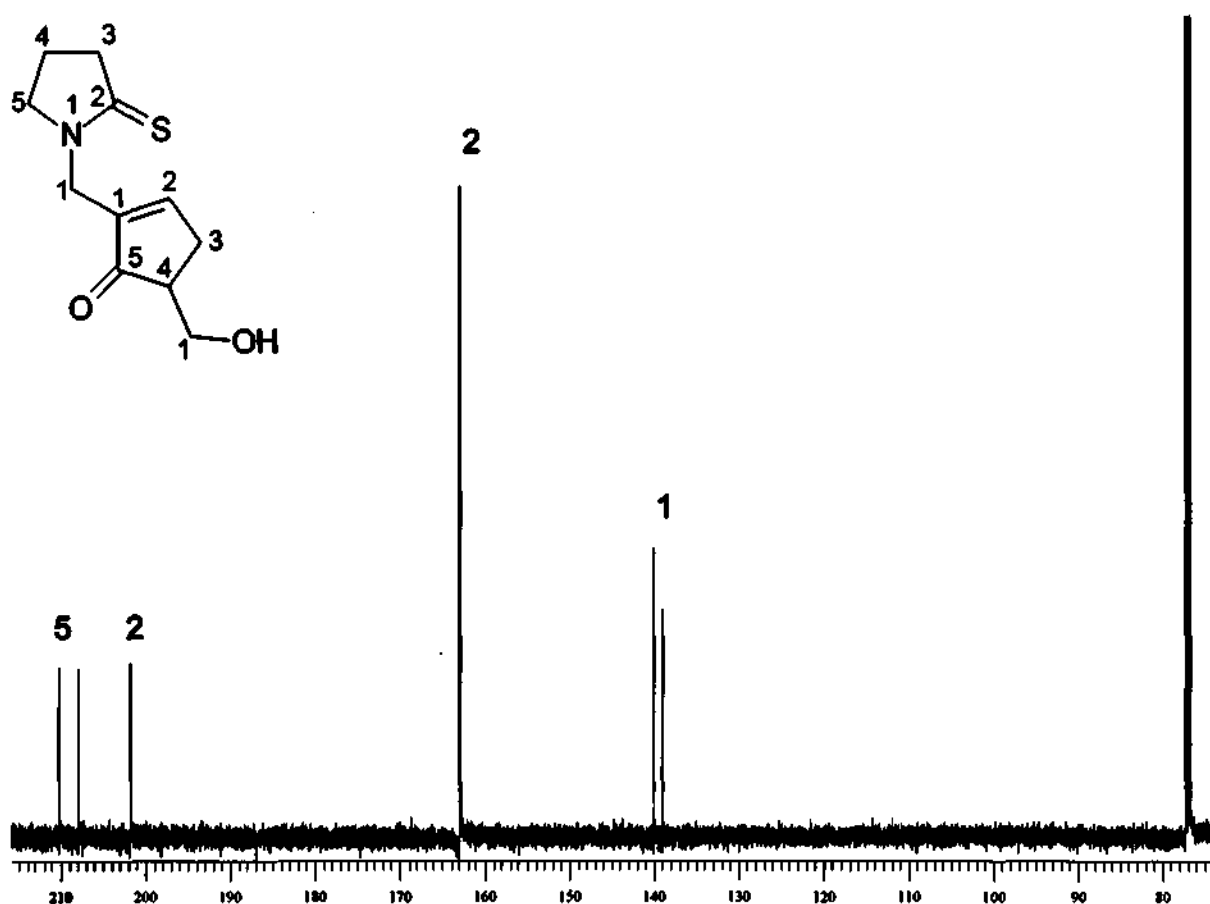
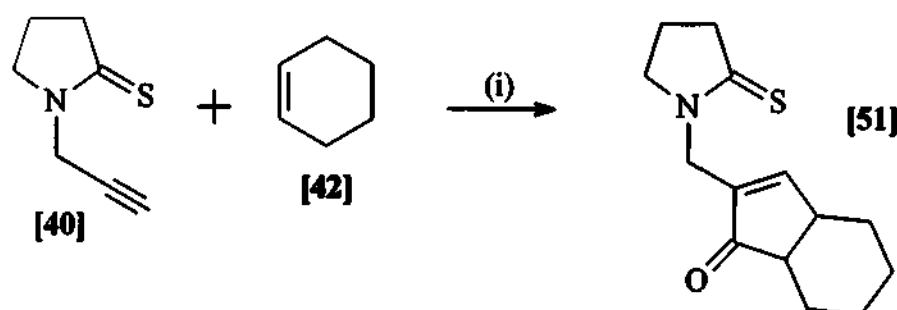


Figure 2.8 ¹³C NMR spectrum of 5-(hydroxymethyl)-2-[(2-thioxo-1-pyrrolidinyl)methyl]-2-cyclopenten-1-one [50] in CDCl₃

repetition. Although the signals relevant to the newly-formed cyclopentenone ring will be highlighted. In Figure 2.8 the quaternary carbon (C_1) of the cyclopentenone ring is observed at 140 ppm and the vinyl carbon (C_2) at 163 ppm. The carbonyl signal (C_5) resonates at 210 ppm while the thiocarbonyl gives rise to a characteristic signal at 202 ppm. Thus, all the signals that pertain to the cyclopentenone ring have been accounted for. HRMS results yielded a mass of 225.08235, which is in good agreement with the calculated mass of 225.08268 a.m.u.

2.2.3 Cyclohexene [42]



Scheme 2.9 (i) $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2 ; 12%.

After 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione and $\text{Co}_2(\text{CO})_8$ were combined in dichloromethane and stirred for half an hour, cyclohexene and NMO were introduced to the reaction mixture.³⁴ This afforded the desired product [51] as a yellow oil in a 12% yield. Formation of 2-[(2-thioxo-1-pyrrolidinyl)methyl]-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one [51] was confirmed by ^1H and ^{13}C NMR spectral data.

Formation for the cyclopentenone ring was confirmed by the signals assigned in Figure 2.9. The carbonyl signal (C_1) resonates at a characteristic 208 ppm while the thiocarbonyl gives rise to a signal at 203 ppm. The quaternary carbon (C_2) of the cyclopentenone ring gives rise to a signal observed at 139 ppm and the vinyl carbon (C_3) at 162 ppm. Once

again, all the signals that pertain to the formation of the cyclopentenone ring have been accounted for.

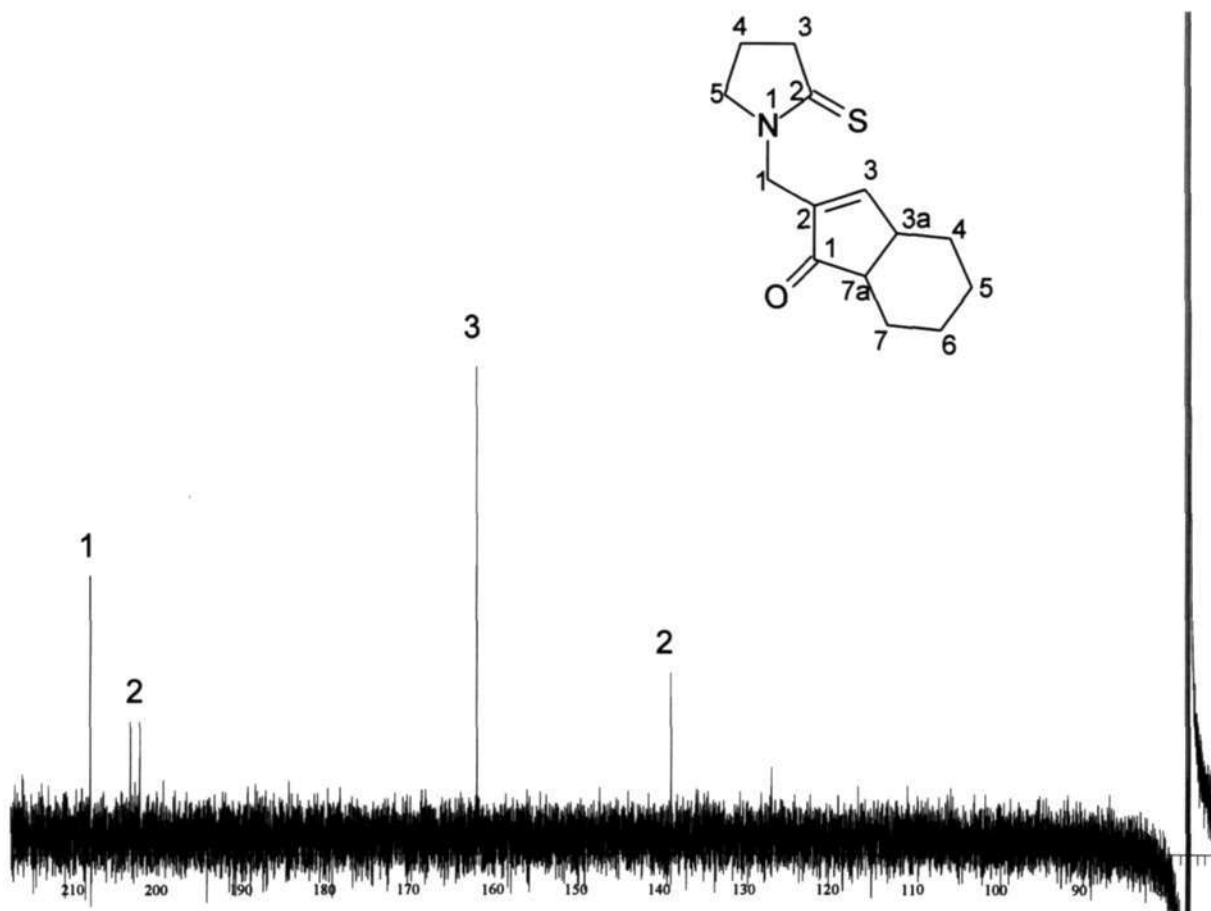
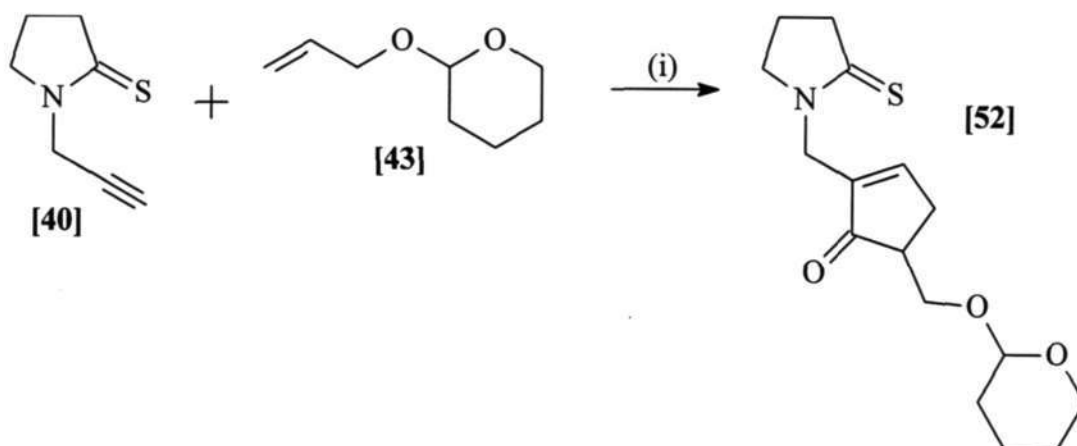


Figure 2.9 ^{13}C NMR spectrum of 2-[(2-thioxo-1-pyrrolidinyl)methyl]-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one [51] in CDCl_3

2.2.4 Tetrahydro-2-(2-propenyloxy)pyran [43]

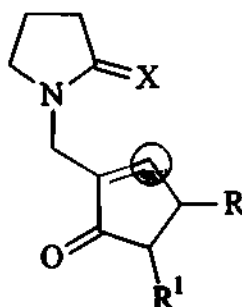


Scheme 2.10 (i) Co_2CO_8 , NMO , CH_2Cl_2 ; 10%.

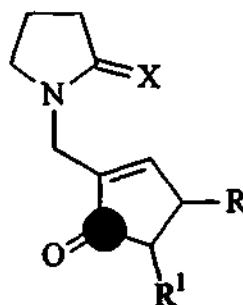
The formation of tetrahydro-2-(2-propenyloxy)pyran was accomplished as noted in section 2.1.4.⁴⁰ The familiar procedure of forming the alkyne-cobalt complex by mixing 1-(2-propynyl)tetrahydro-2*H*-pyrrole-2-thione [40] and dicobalt octacarbonyl in CH₂Cl₂ was applied. NMO and tetrahydro-2-(2-propenyloxy)pyran [43] were then added to the mixture. 5-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]-2-[(2-thioxo-1-pyrrolidinyl) methyl]-2-cyclopenten-1-one [52] was obtained in a 10% yield as a yellow oil.

Unstrained cyclic alkenes are generally less reactive than strained cyclic alkenes.²⁶ Whilst alkenes with electron withdrawing groups generally give low yields for the Pauson-Khand reaction by reacting anomalously to produce 1,3-dienes.²⁶ These two trends for the Pauson-Khand reaction could account for the lower yields using allyl alcohol and cyclohexene as alkenes compared to norbornadiene.

To avoid any further tautology with regard to the assignment of signals arising from the cyclopentenone ring, there are some observations that need to be mentioned. These pertain to the chemical shifts for the vinyl carbon NMR signal obtained for the successfully synthesized Pauson-Khand products using 1-(2-propynyl)tetrahydro-2*H*-pyrrole-2-thione as the starting material and the various alkenes. The success of the Pauson-Khand reaction can be quickly determined by the appearance of the vinyl carbon NMR signal at approximately 162-164 ppm and a corresponding vinyl proton NMR signal from about 7.5 to 7.8 ppm.



A similar trend is observed with the ^{13}C NMR signal of the carbonyl carbon of the cyclopentenone ring. This carbon gives rise to a signal in the 207-210 ppm region. Thus this characteristic signal can also be used to rapidly determine if the formation of the cyclopentenone ring system was successful.



2.3 Discussion of Results

The difference in yields between the lactam [39] and thiolactam [40] is summarized in Table 2.1. To provide a frame of reference the typical yields of a Pauson-Khand reaction are in the 30-60% range.²⁶

Table 2.1 *Comparison of yields between 2-(2-propynyl)tetrahydro-2H-pyrrol-2-one [lactam] and 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [thiolactam] with various alkenes*

<u>Alkene</u>	<u>Lactam</u>	<u>Thiolactam</u>
Norbornadiene	42%	62%
Allyl Alcohol	No product	10%
Cyclohexene	No product	12%
Protected Allyl Alcohol	No product	10%

It immediately becomes apparent that the Pauson-Khand reaction does not behave in the same manner for lactam and thiolactam. However, the only change between the

compounds is the conversion from a carbonyl to a thiocarbonyl. At first it was thought that there could be a possible electronic effect, due to the influence of the sulfur atom, which alters the reactivity of the alkyne triple bond. After several semi-empirical calculations (Table 2.2) using PC Spartan Pro, no significant electronic changes occurred within the triple bond. The calculations were performed to determine the charge upon each atom of the propargyl chain for the lactam and thiolactam. The results are given in Table 2.2. There is no significant change in the charge upon the three carbon atoms in question. The carbonyl and thiocarbonyl are too spatially remote from the alkyne bond to have any significant impact on the electronic properties of the triple bond. Figure 2.6 is an image of the LUMO of 2(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39] generated from the calculations performed. The negative LUMO is depicted in green and the positive LUMO is highlighted in purple. There was little difference between the LUMO and HOMO for both the lactam and thiolactam *N*-propargyl groups. The variations were not significant enough to account for the discrepancy in the yields.

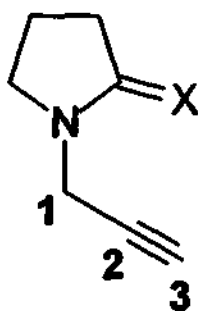


Table 2.2 *Calculated charges on the propargyl carbons of the lactam and thiolactam starting materials*

Carbon	1	2	3
Lactam	0.094 kcal/mol	0.026 kcal/mol	-0.298 kcal/mol
	0.408 eV	0.113 eV	-1.292 eV

Thiolactam	0.115 kcal/mol	-0.017 kcal/mol	-0.259 kcal/mol
	0.500 eV	-0.074 eV	-1.123 eV

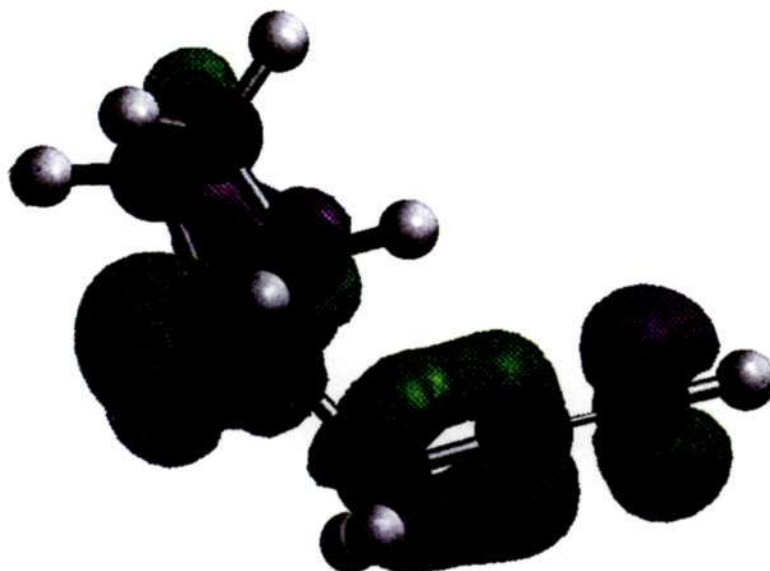
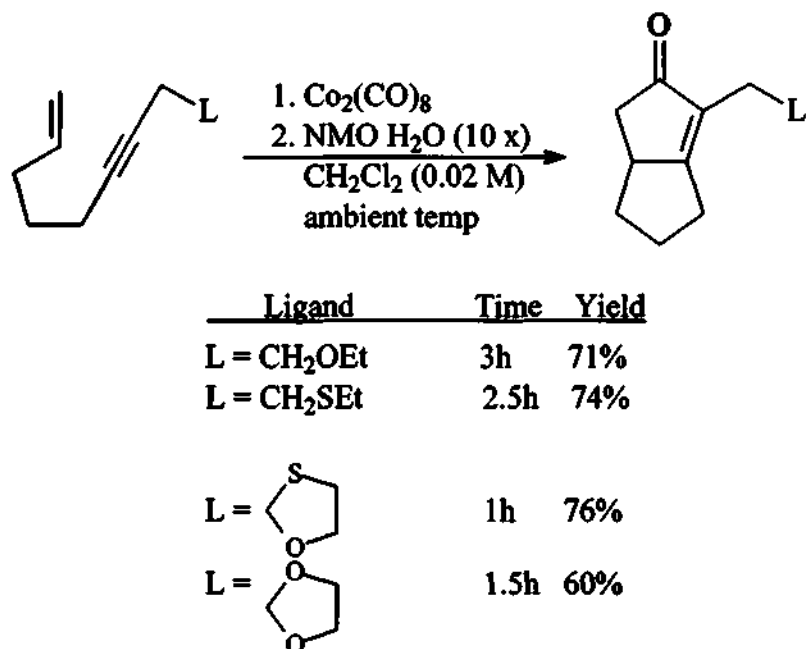


Figure 2.7 The calculated LUMO of 2(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39]

There were also no physical property changes that could account for this discrepancy such as a marked change in solubility. It has been noted that cobalt(0) does coordinate to soft ligands, such as nitrogen and sulfur. This aspect of the Pauson-Khand reaction has been pursued by Krafft [Scheme 2.11].⁴¹ While investigating the efficacy of oxygen, nitrogen and sulfur as directing ligands, for the Pauson-Khand reaction, it was noted that both sulfur and nitrogen provided excellent regiocontrol. The methoxymethyl ethers and alcohols did not provide any regioselectivity. Heteroatom coordination is now widely used for stereocontrolled Pauson-Khand reactions.^{42, 43} Krafft observed in later investigations that the greatest increase in reaction rates and yields occur in reactions with sulfur and nitrogen ligands.⁴⁴ The presence of a sulfur ligand in an amine oxide promoted reaction leads to the

stabilization of a pentacarbonyl intermediate and hence, improved yields of a sulfur ligand over an oxygen ligand. The exact mechanism for this is either due to promoted CO



Scheme 2.11

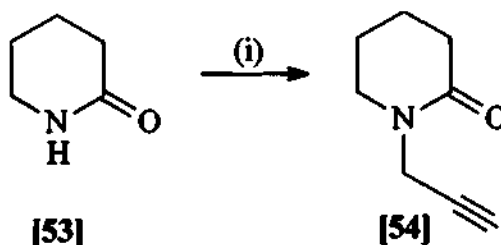
insertion when a tetracarbonyl complex is formed, or the inhibition of decarbonylation of the pentacarbonyl complex due to the heteroatom. Thus, it is most possible that a similar situation has occurred with the alkynes used in this experiment. The sulfur atom of the thiocarbonyl (sulfur-softer ligand) is positioned at a distance where coordination to the cobalt atom could take place. This in turn would stabilize the intermediate complex more effectively than the lactam carbonyl (oxygen-harder ligand) and thus improve the yield of the reaction. Hence, the yield of 42% for the lactam and norbornadiene compared to a yield of 62% for the thiolactam and norbornadiene. Unfortunately, isolation of such an intermediate proved unsuccessful. Interestingly, such attempts by Krafft *et al.* proved similarly unrewarding. Such intermediates are so unstable that no crystal structure has been collected of such a compound.

CHAPTER 3

PROGRESS TOWARDS THE SYNTHESIS OF DENDROBATID ALKALOID 251F

3.1 Synthesis of 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [54]

To obtain the desired starting material for the Pauson-Khand reaction, δ -valerolactam was first propargylated [Scheme 3.1]. This was achieved by mixing propargyl bromide with δ -valerolactam [53] in THF using sodium hydride as base. When the reaction was performed at ambient temperature or even 0°C the mixture bubbled vigorously and very poor yields were obtained. It was then decided to perform the reaction at -78°C, in an acetone/carbon dioxide bath. 1-(2-Propynyl)tetrahydro-2(1H)-pyridinone [54] was formed as a yellow oil in 65% yield under these conditions.



Scheme 3.1 (i) NaH, propargyl bromide, THF, -78°C, 65%.

^1H and ^{13}C NMR spectroscopic evidence confirmed that 1-(2-propynyl)tetrahydro-2(1H)-pyridinone [54] had been formed.⁴⁵ Figure 3.1 shows the ^1H NMR spectrum with integration. The large singlet at 4.12 ppm that integrates for two protons was assigned to C_1 . The signal appearing at 3.31 ppm was assigned to the protons attached to C_6 due to it being adjacent to the electron-withdrawing nitrogen atom. The signal correlating to the

protons of C₃ was assigned to the signal appearing at 2.3 ppm. This was corroborated by GHMQC evidence showing a very strong correlation from this proton signal and that of the carbonyl carbon (C₂). The singlet at 2.1 ppm integrates for a single proton and was therefore assigned to C₃ the terminal alkyne carbon. The multiplet that extends from 1.7 ppm to 1.8 ppm was assigned to the two H₂'s C₄ and C₅.

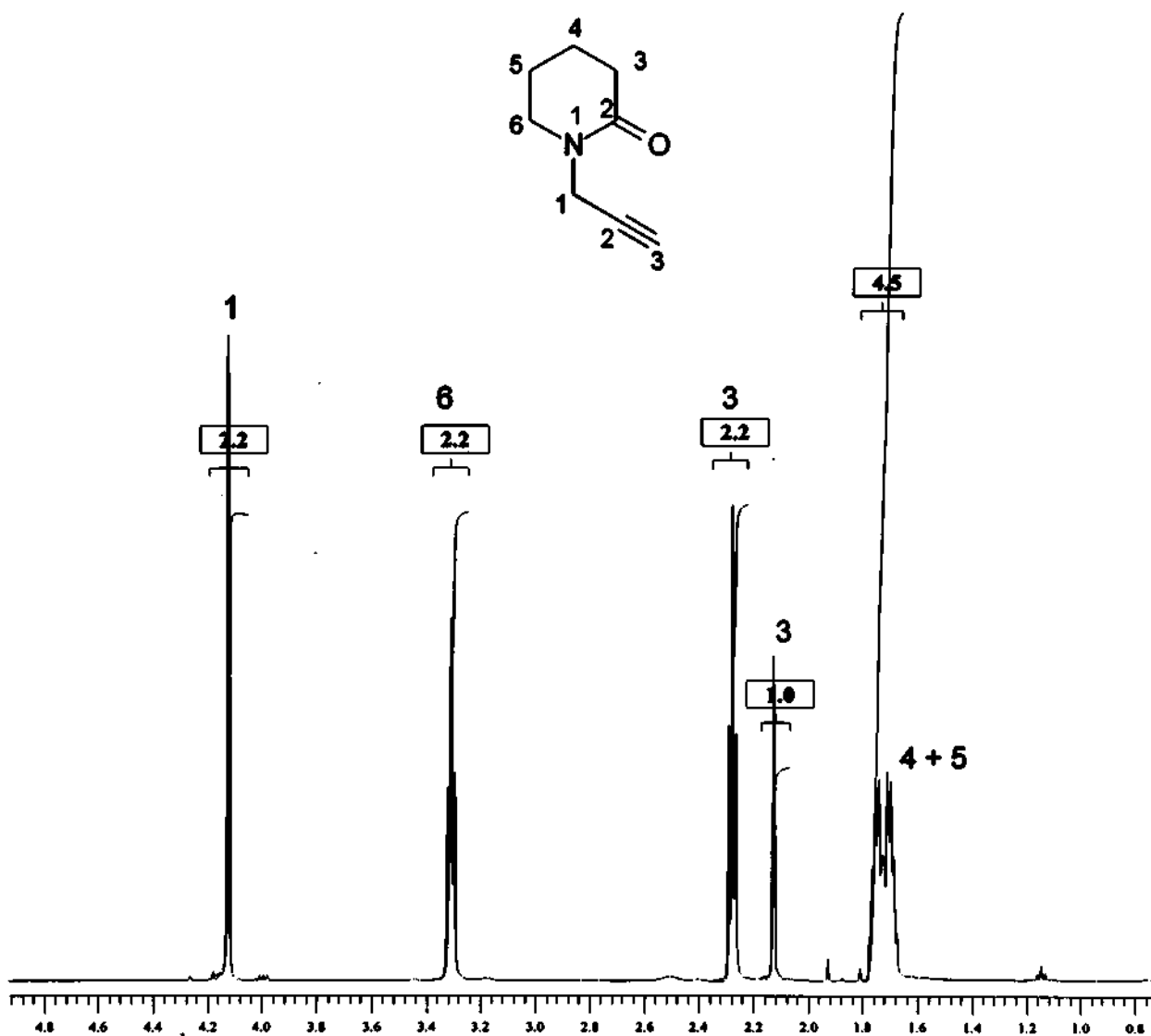
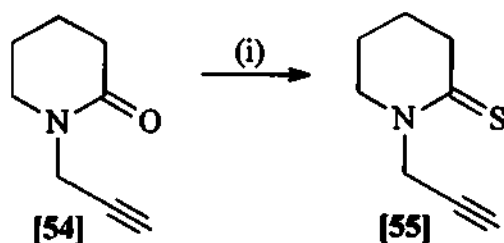


Figure 3.1 ¹H NMR spectrum of 1-(2-propynyl)tetrahydro-2(1H)-pyridinone [54] in CDCl₃

Next 1-(2-propynyl)tetrahydro-2(1H)-pyridinone [54] had to be thionated to obtain a similar starting material to that used for the methodological study presented in Chapter 2.

As observed previously, it was advantageous to use a thiolactam as the starting material because they appear to give better results in the Pauson-Khand reaction. Thus, thionation was attempted, using the procedure previously established in our lab⁴⁶, by adding the propargylated lactam [54] to a stirred mixture of sodium carbonate and phosphorus pentasulfide in dry THF. The reaction mixture was left to stir overnight but thionation did not take place and the starting material [54] was recovered in a 64% yield. It was noted in our lab, from previous work, that once δ -valerolactam has been propargylated, thionation would not take place and conversely that once δ -valerolactam had been thionated the propargylation reaction would not occur. Although this conclusion was drawn from experiences using phosphorus pentasulfide³⁹ as well as Lawesson's reagent with established procedures³⁶ an intriguing alternative using a microwave reaction was attempted. Our laboratory has successfully optimised the procedure developed by Hamelin and co-workers⁴⁷ for use with various vinylogous urethanes and amides⁴⁸. The experiment was conducted in a commercial microwave with the lactam starting material [54] and Lawesson's reagent simply mixed together in a polytop vial. The vial (with contents) was placed on a bed of alumina, which was placed in the microwave and heated for twenty seconds on low power [Scheme 3.2]. The material was then extracted with



Scheme 3.2 (i) Lawesson's reagent, microwave irradiation; ~70%.

dichloromethane with only the desired product [55] and an unidentifiable by-product formed. There was a 92% mass recovery with approximately 70% of this being 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55]⁴⁹. All of the starting material [54] had reacted in those twenty seconds! In Chapter 2 the issue of the instability of propargylated thiolactams was raised and again this was a serious concern. After purification, formation of the product was confirmed using NMR spectroscopy, but this also highlighted how quickly the thiolactam decomposed. It was thus decided that no purification would be done after the microwave reaction. The dichloromethane extract would simply be filtered and immediately added to the next reaction.

Figure 3.2 shows the ¹³C NMR spectrum which is used to confirm the formation of 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] as the signals in the ¹H spectrum of the lactam and thiolactam overlap significantly. The very intense signals in Figure 3.2 are for 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinone [54]; the vertical scale of the spectrum was increased so the signals relevant to 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] could be labeled. This is due to approximately 80% of the sample reverting to the lactam in the four hours it took to acquire the NMR data for the sample. Thanks to our prior experience with the spectra for the corresponding five-membered ring it was a relatively simple task to assign the signals. The thiocarbonyl (C₂) was easily identified as the peak at 200.1 ppm. The signal for the terminal alkyne (C₃) appeared, as expected, at 78.2 ppm and the signal for the other alkyne carbon (C₂) gave a corresponding signal at 72.7 ppm. Due to the rapid decomposition of 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] no IR spectra or HRMS results could be obtained.

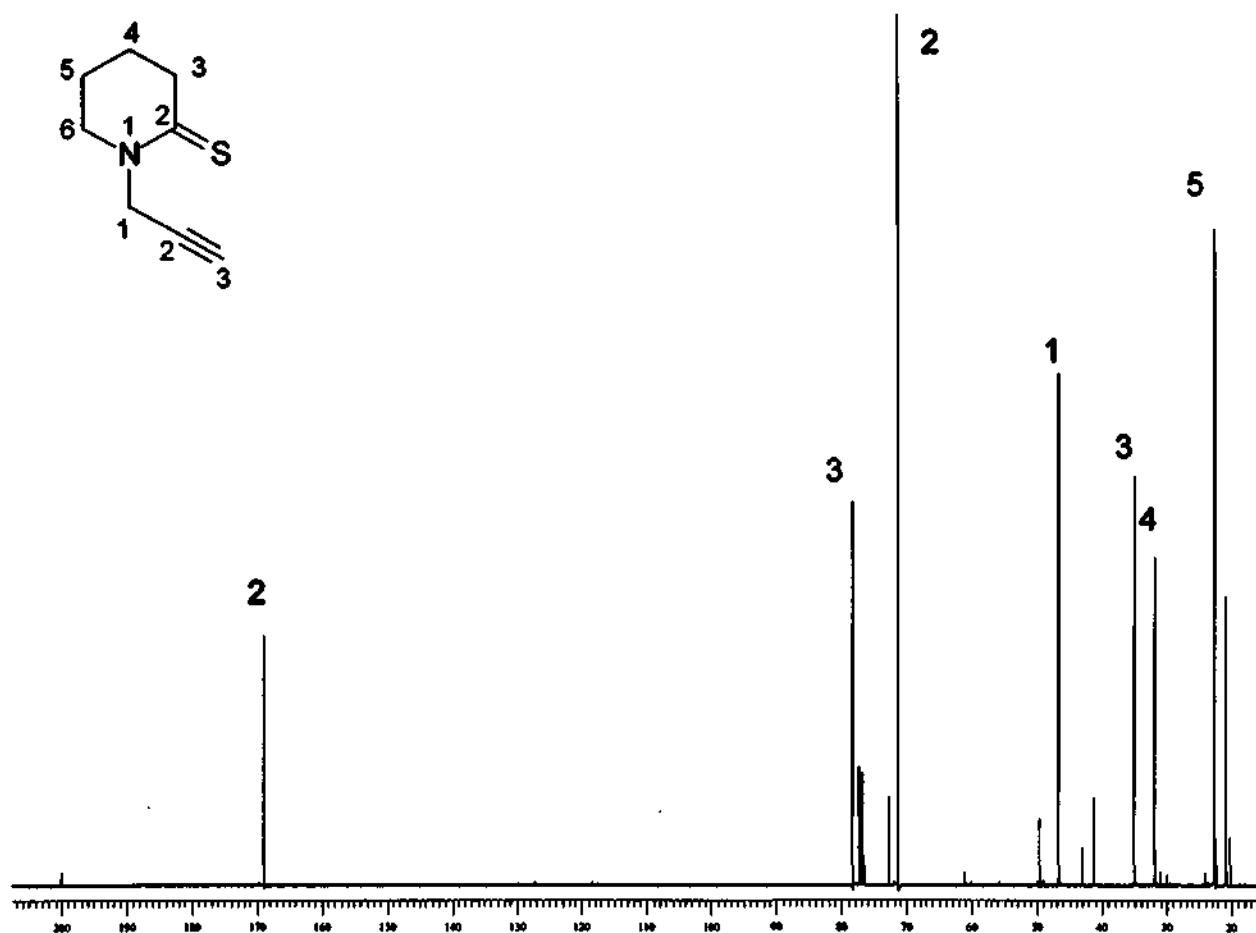
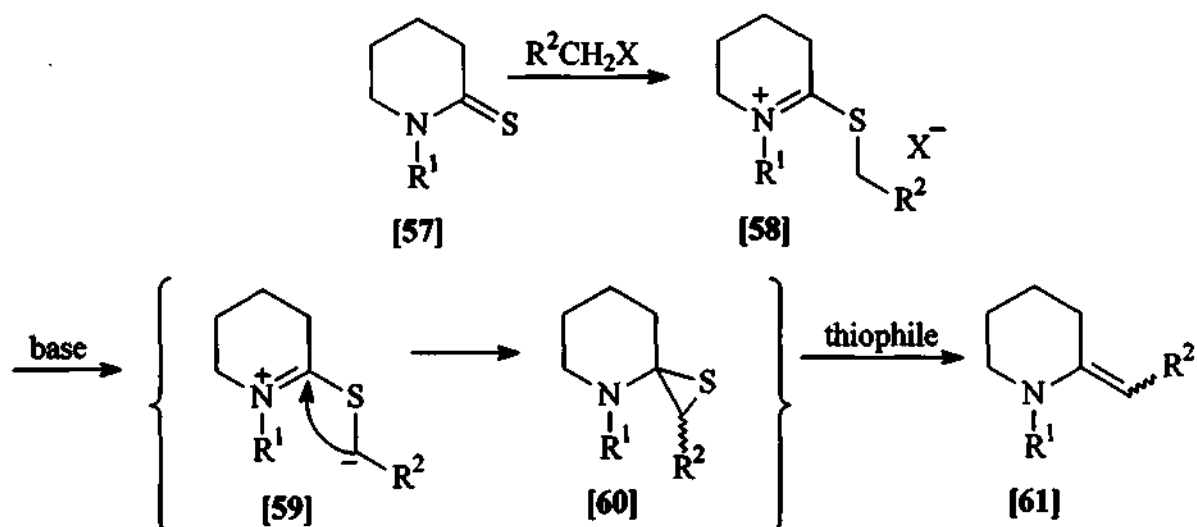


Figure 3.2 ^{13}C NMR spectrum of 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [55] in CDCl_3

3.2 Attempted synthesis of ethyl 2-(1-([(1R,7S)-5-oxotricyclo [5.2.1.0^{2,6}]deca-3,8-dien-4-yl)methyl]-2-piperidinylidene)acetate [56]

Now that we had a means of rapidly synthesising 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [55] we were in a position to attempt the Pauson-Khand reaction. Due to fears of decomposition, the product of the Pauson-Khand reaction would not be purified but instead carried over into a subsequent Eschenmoser sulfide contraction reaction [Scheme 3.3]. In this way it was hoped we would obtain our desired vinylogous urethane [56].

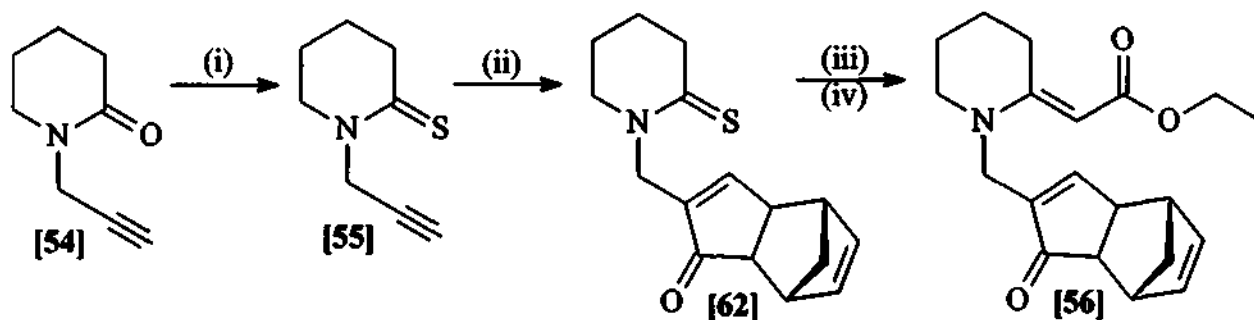
The Eschenmoser sulfide contraction [Scheme 3.3] is a versatile and efficient method of preparing vinylogous urethanes. Alkylation of a secondary or tertiary thioamide with an appropriate electrophilic component takes place and is followed by the elimination of sulfur. The reaction itself is composed of two steps. Initially the thioamide [57] is



Scheme 3.3 Mechanism of Eschenmoser Sulfide Contraction, R^2 = electron-withdrawing group.

chemoselectively alkylated on the sulfur with an electrophile to form an intermediate α -thioiminium salt [58]. In the second step a base and sulfur scavenger (thiophile) are added to promote the extrusion of sulfur with concomitant formation of a π -bond. According to the accepted mechanism, in the second step of the reaction, the base abstracts an α -proton from the appended side chain of the α -thioiminium salt. This generates an anion [59] which is then captured by the iminium species to form an episulfide [60]. This intermediate then collapses with the assistance of a thiophile, which extrudes sulfur to produce the unsaturated product [61].

Synthesis of ethyl 2-(1-{{[(1*R*, 7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl} -2-piperidinylidene)acetate [56] [Scheme 3.4] was attempted by first synthesising 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] by using the microwave reaction. The product was extracted with dichloromethane, filtered and immediately added to the reaction vessel under a nitrogen atmosphere. The appropriate amount of dicobalt octacarbonyl was added shortly afterwards to form the intermediate cobalt complex of the

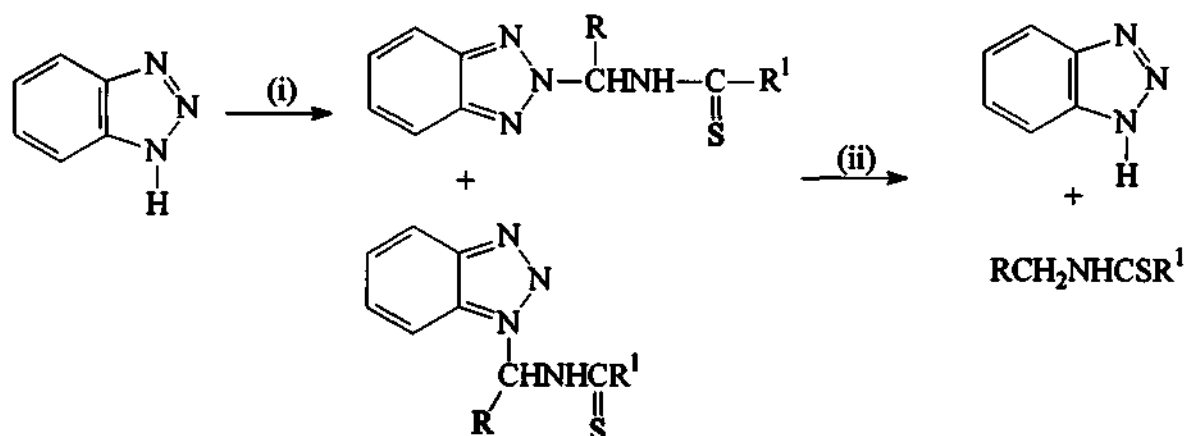


Scheme 3.4 Proposed synthetic route (i) Lawesson's reagent, microwave irradiation; (ii) $\text{Co}_2(\text{CO})_8$, norbornadiene, NMO; (iii) $\text{BrCH}_2\text{CO}_2\text{Et}$; (iv) CH_3CN , Et_3N , Ph_3P .

Pauson-Khand reaction. After stirring at room temperature the reaction vessel was cooled and norbornadiene [37] was added along with NMO. The reaction mixture was allowed to warm to ambient temperature and left to stir overnight. The mixture was run through a silica gel plug to remove the cobalt residues. The extract was concentrated *in vacuo*, dissolved in a minimum amount of acetonitrile and immediately placed under a nitrogen atmosphere. Formation of the α -thiiminium salt was achieved using ethyl bromoacetate and monitored using TLC. Once maximum salt formation had taken place triethylamine and triphenylphosphine dissolved in dichloromethane were introduced, to act as base and thiophile respectively. No product [56] was obtained and no starting materials were recovered. Based on TLC evidence the lability and decomposition of the starting material

1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] is proposed to account for this disappointing result.

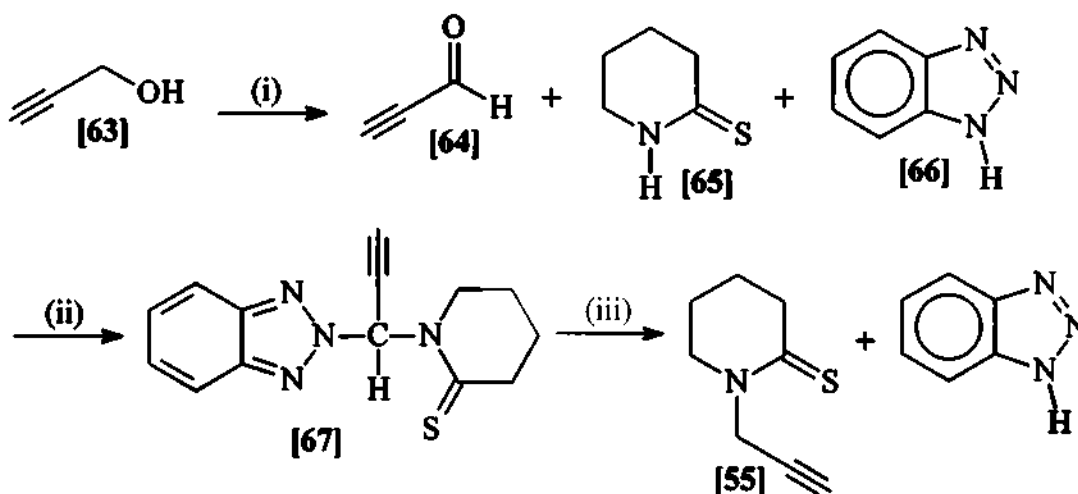
An alternative method for the *N*-alkylation of thioamides by Katritzky and Drewniak⁵⁰ was explored. In this procedure [Scheme 3.5] aldehydes together with thioamides are treated with benzotriazole in toluene. The reaction mixture is refluxed with azeotropic removal of water. This affords *N*-[1-(benzotriazol-1-yl)alkyl]thioamide adducts which are then reduced to the corresponding *N*-alkylthioamide by sodium borohydride. The thioamides used in the experimental work were thiobenzamide, thiourea and thioisonicotinamide. An even greater variety of aldehydes were investigated, namely propanal, isopropanal, pentanal, heptanal, octanal, undecanal and nonanal.



Scheme 3.5 (i) R¹CSNH₂; (ii) NaBH₄

To obtain the correct aldehyde that would afford 1-propynyltetrahydro-2(1*H*)-pyridinethione [55], propargyl alcohol [63] had to be oxidised to propynal [64] [Scheme 3.6]. This was achieved using a procedure where the alcohol [63] is dissolved in ethyl methyl ketone and a solution of chromium trioxide, sulfuric acid and water is added dropwise, over one hour to the mixture.⁵¹ Propynal was obtained by oxidising propargyl alcohol with chromium trioxide and sulfuric acid. Equimolar amounts of propynal [64],

thioamide [65] and benzotriazole [66] were heated together under reflux in toluene overnight.⁵⁰ Water was removed from the reaction as an azeotrope using a Dean and Stark apparatus. Unfortunately we were never able to form adduct [67]. This was confirmed by TLC and NMR evidence. The starting materials were all present at the end of the period of



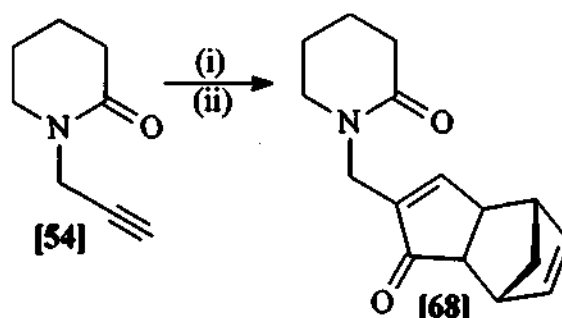
Scheme 3.6 (i) CrO_3 , H_2SO_4 ; (ii) toluene, reflux; (iii) NaBH_4

reflux. This suggests that the cyclic thioamide [65] is too sterically hindered or too different electronically to the examples used in the literature precedent to form the desired adduct [67] in any appreciable amount.

However, to ensure that the method we were using to perform the Pauson-Khand was not at fault due to concerns that the five- and six-membered ring systems might require different conditions, we performed the Pauson-Khand reaction on 1-(2-propynyl)tetrahydro-2(1H)-pyridinone [54].

3.3 Synthesis of 1-(((1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4yl)methyl) tetrahydro-2(1H)-pyridinone [68]

The propargylated lactam 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinone [54] was dissolved in dichloromethane and placed under nitrogen [Scheme 3.7]. Dicobalt octacarbonyl was then added to the reaction vessel. Carbon dioxide was evolved from the reaction mixture, which was left to stir at room temperature. After cooling, an appropriate amount of norbornadiene and NMO were added. The mixture was allowed to warm to ambient temperature and left stirring overnight. The solid cobalt residues were removed by washing the mixture through a silica gel plug and the extract concentrated *in vacuo* before being purified by radial chromatography. 1-{[(1*R*,7*S*)-5-Oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4yl]methyl}tetrahydro-2(1*H*)-pyridinone [68] was obtained as a yellow oil in 24% yield. The structure of the product was verified by ¹³C and ¹H NMR spectroscopic data.



Scheme 3.7 (i) Co₂(CO)₈, CH₂Cl₂; (ii) 0 °C, norbornadiene, NMO; 24%.

Due to the similarities between 1-{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44] and 1-{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4yl]methyl}tetrahydro-2(1*H*)-pyridinone [68] some signals were easy to identify. For example, in the ¹H spectrum [Figure 3.3] the vinyl proton at C₃ is the farthest signal downfield, resonating as expected at 7.3 ppm. The two signals appearing at 6.2 and 6.1 ppm represent the vinyl protons of the norbornadiene double bond attached to carbons C₉ and C₈ respectively. The singlet which integrates for two protons, at 4.1 ppm, is clearly due

to the protons at C₁. The two signals farthest upfield at 1.16 and 1.15 ppm that integrate for approximately one proton each represent the protons on the norbornadiene bridge (C₁₀) occupying sufficiently different environments so as to render them magnetically non-equivalent with one above the plane of the carbon-carbon double bond. This was confirmed by the GHSQC spectrum which showed each ¹H signal correlating strongly with the same signal in the ¹³C spectrum. Thus C₂ was subsequently identified in the ¹³C spectrum at 42 ppm. The DEPT experiments showed that the same carbon signal

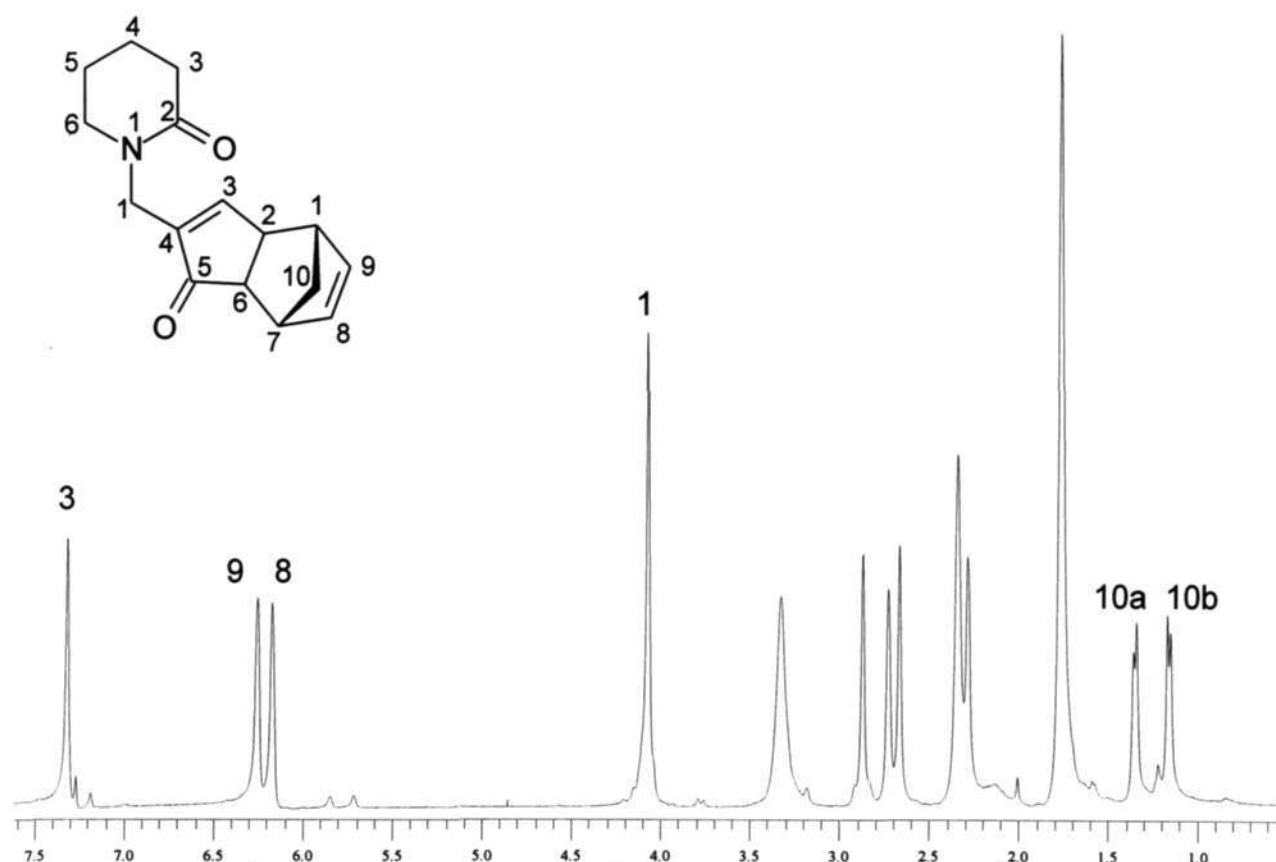


Figure 3.3 ¹H NMR spectrum of 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [68]

had two protons. The downfield signals of the ¹³C spectrum [Figure 3.4] were almost identical to those obtained for 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [68]. The signal appearing at 209 ppm corresponds to the

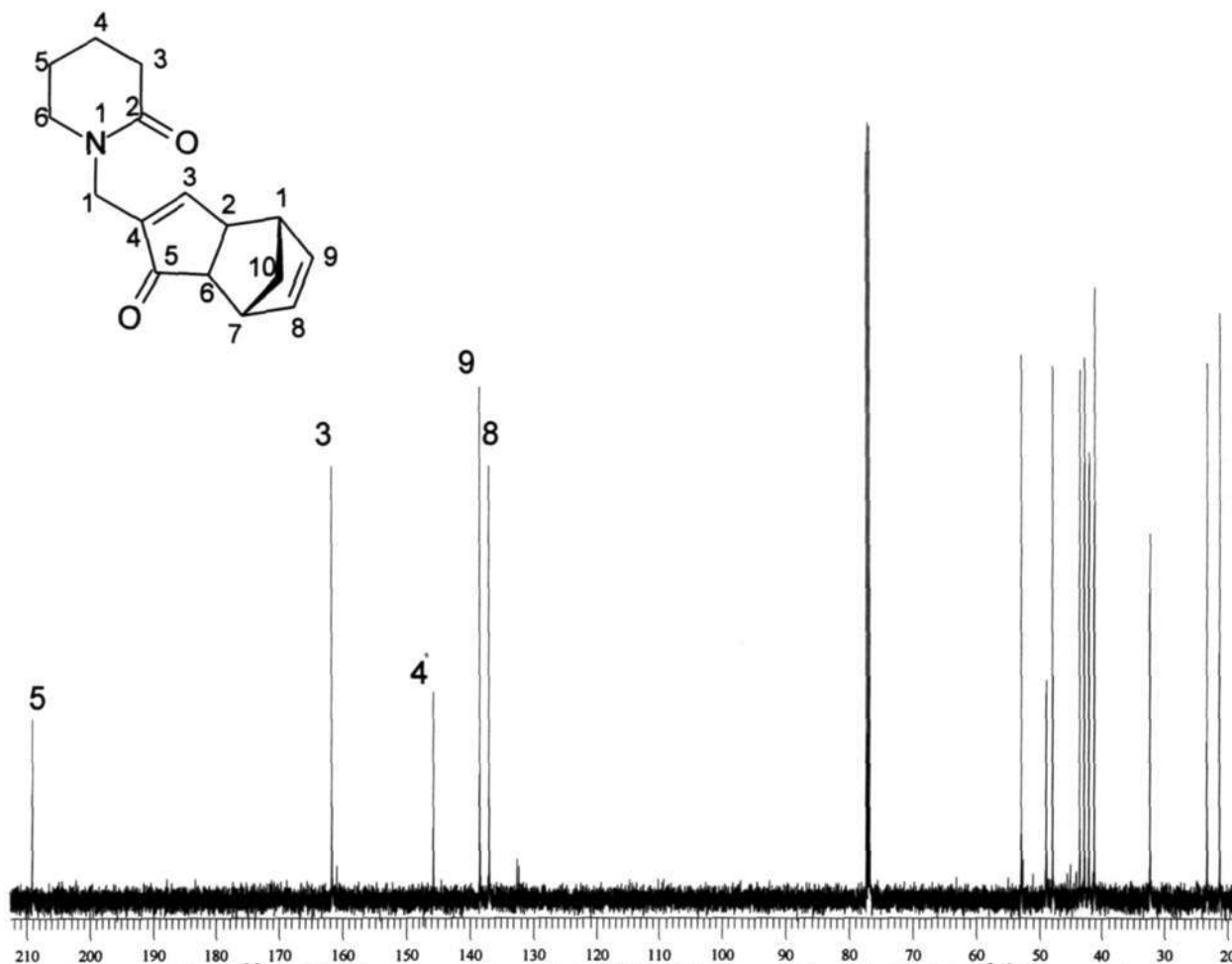


Figure 3.4 ^{13}C NMR spectrum of 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [68]

carbonyl carbon of C₅, and a DEPT experiment confirmed this signal was produced by a quaternary carbon. The signal at 162 ppm corresponded to C₃ and this was corroborated by DEPT experiments showing this carbon is bonded to a single proton (the vinyl proton), and GHSQC data showing a strong correlation between the proton signal at 7.3 ppm (previously assigned to the proton attached to C₃) and this same carbon signal. The signal at 146 ppm was shown to be a quaternary carbon which appears too far upfield to account for the carbonyl carbon (C₂). GHMQC [Figure 3.5] experiments showed long-range coupling from the ^1H signal of C₁ to the carbon signals of C₅, C₃ and the carbon signal in question. Thus, the signal was determined to be that of C₄. The next two signals were shown by DEPT spectra to have one proton each. There are only two vinyl carbons

remaining unaccounted for at this stage; those attached to C₉ and C₈. This was substantiated by GHSQC data showing a strong correlation from the respective proton signals at 6.2 and 6.1 ppm and these ¹³C NMR signals. The signal for C₉ appears at 138 ppm and that of C₈ appears at 137 ppm. The missing signal is, of course, that of the carbonyl carbon of C₂.

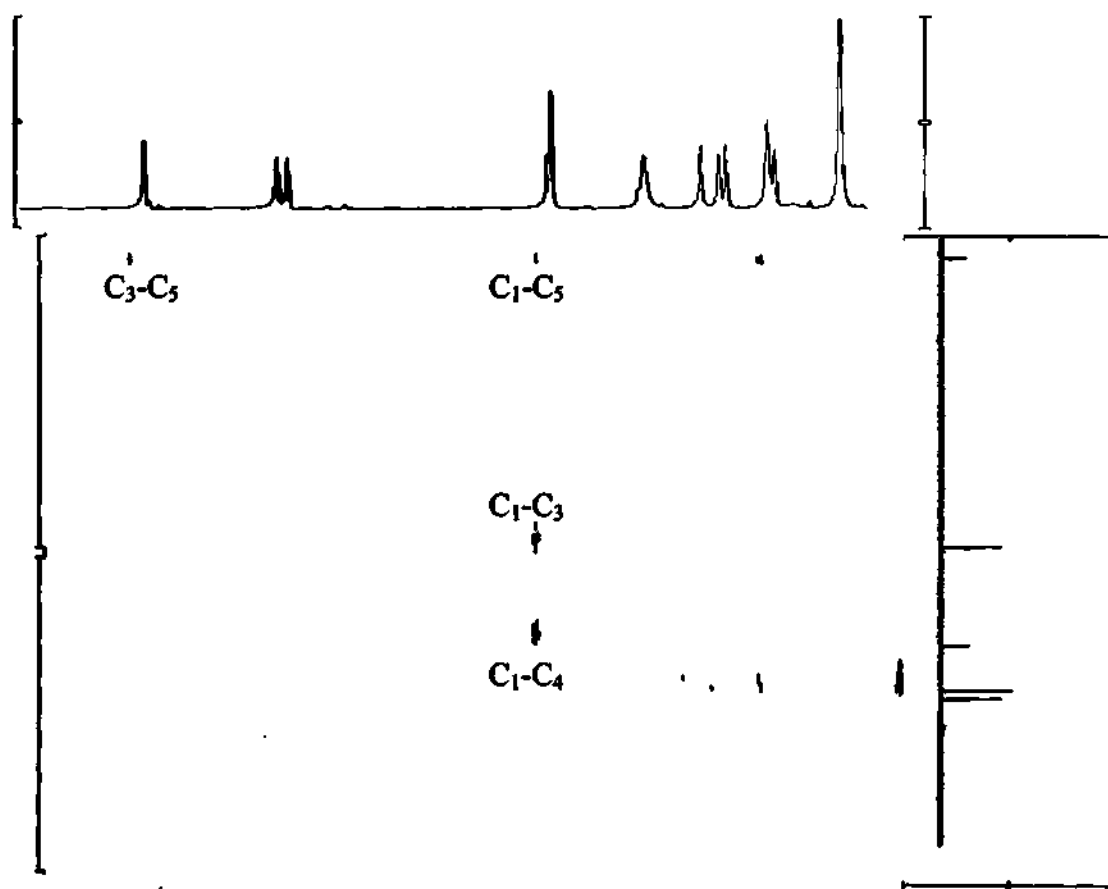
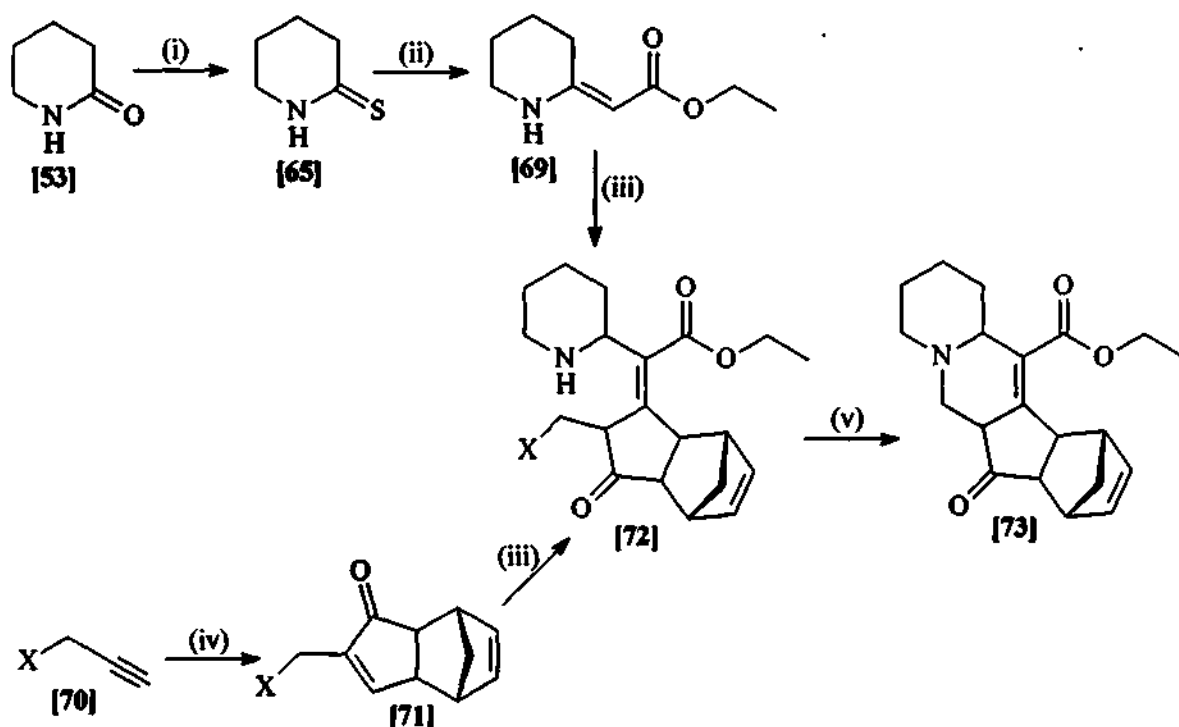


Figure 3.5 GCHMQC NMR spectrum of 1{[(1R,7S)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [68]

so weak that it was not detected in the NMR experiments performed. The signals that have been discussed pertain to the formation of the cyclopentenone ring and confirm that the Pauson-Khand reaction was a success. HRMS results yielded a mass of 257.14158, which is in good agreement with the calculated mass of 257.14153 a.m.u.

Although we were encouraged to see that the Pauson-Khand reaction was successful, it was felt that even if we were to thionate the C₁ carbonyl the compound would still be too unstable to survive the Eschenmoser sulfide contraction reaction. In order to avoid such unstable compounds the synthetic route was altered. A convergent synthesis [Scheme 3.8] was devised. The lactam [53] would be thionated to give thiolactam [65] and an Eschenmoser sulfide contraction would be performed to give [69]. The other moiety would be synthesised using the Pauson-Khand reaction on a propargyl compound [71]. Compound [72] would then be prepared by conjugate addition of the enolate derived from [69] to enone [71] and cyclisation would then be effected [72] by exploiting the enaminic reactivity of vinylogous urethanes to perform a conjugate addition reaction to the α,β -unsaturated ketone functionality. The final ring would then be closed [73] by nucleophilic

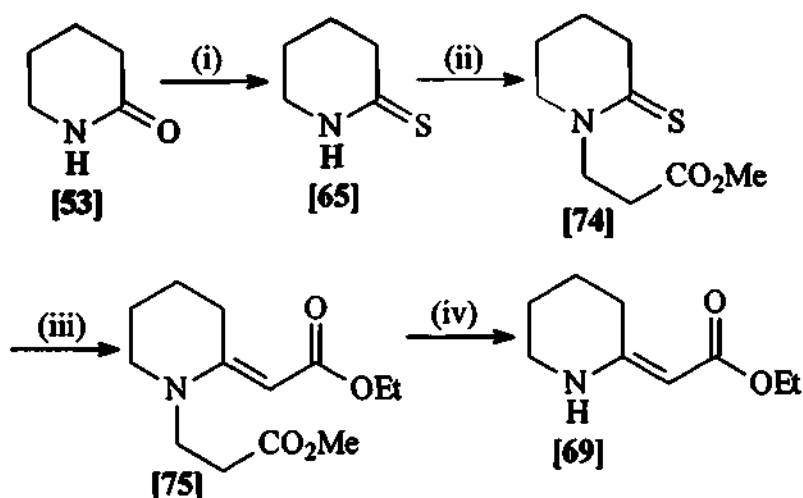


Scheme 3.8 Proposed reaction sequence (i) thionation; (ii) Eschenmoser sulfide contraction; (iii) conjugate addition reaction; (iv) Pauson-Khand reaction, norbornadiene; (v) cyclisation by displacement of a suitable leaving group X.

displacement of a suitable leaving group (X) using an appropriate solvent and base if the cyclisation did not proceed spontaneously.

3.4 Attempted syntheses of ethyl α -(hexahydro pyridylidene-2)acetate [69]

Our expeditious method of using microwave energy to perform thionation reactions was used once again to good effect, but this time to thionate δ -valerolactam [53]. Tetrahydro-2(1*H*)-pyridinethione [65] was produced in 78% yield as a yellow oil [Scheme 3.9]. This

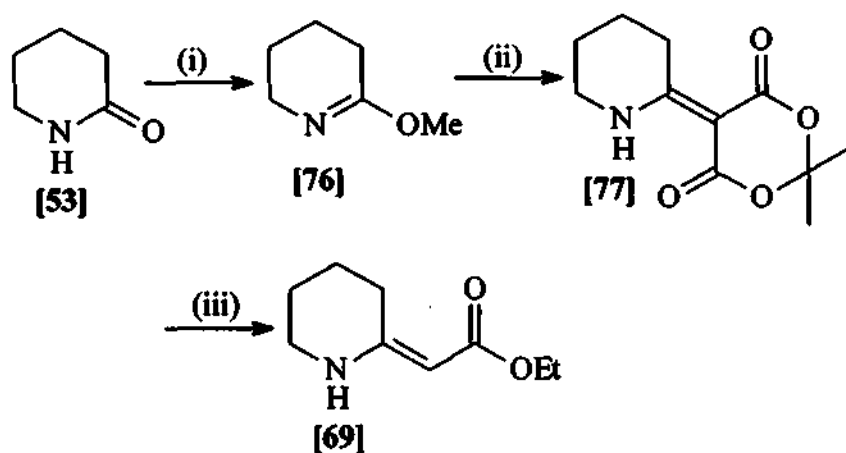


Scheme 3.9 (i) Lawesson's reagent, microwave irradiation; (ii) methyl acrylate, NaOH, THF; (iii) $\text{BrCH}_2\text{CO}_2\text{Et}$, CH_3CN , Et_3N , Ph_3P ; (iv) KHMDS.

was verified by ^{13}C and ^1H NMR spectroscopic data. The next step involved the protection of the secondary thioamide. This was done to prevent reaction of the electrophile of the Eschenmoser sulfide contraction, in this case ethyl bromoacetate, with the secondary thioamide. The secondary amide was therefore converted to a tertiary amide [74] using a base (sodium hydroxide) and methyl acrylate. After the reaction the product was subjected

without further purification to the Eschenmoser sulfide contraction [75]. The salt formation with ethyl bromoacetate was allowed to stir overnight to afford maximum salt formation. Once salt formation was verified by TLC, a solution of triethylamine and triphenylphosphine in dichloromethane was added. TLC at this point revealed that the desired product had not been formed.

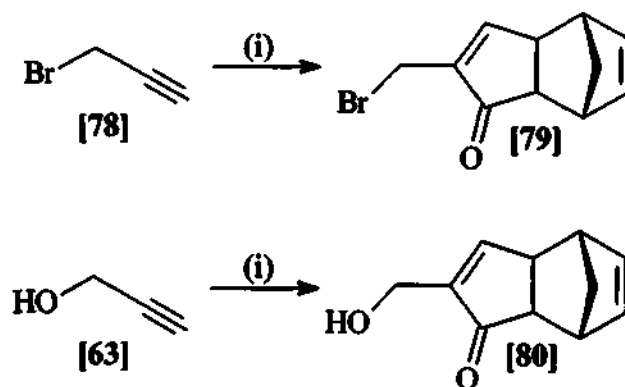
An alternate method utilising lactim ether chemistry was explored. Ethyl α -(hexahydro-2-pyridinylidene)acetate had been successfully synthesised by Maitte⁵² and co-workers using lactim ethers and isopropylidene malonate (commonly called Meldrum's acid). Meldrum's acid was synthesised by adding acetone to a solution of malonic acid, acetic anhydride and a small amount of sulfuric acid.⁵³ This was confirmed by ¹H and ¹³C NMR spectroscopic data. To form the lactim ether, δ -valerolactam [53] was added slowly to dimethylsulfate⁵⁴ at ambient temperature. This mixture then was maintained at a temperature of 60°C and left stirring overnight. Meldrum's acid, triethylamine and more toluene were added to the lactim ether [76] [Scheme 3.10] and refluxed together overnight. The solvent was removed *in vacuo* and isopropylidene α -(hexahydro-2-pyridinylidene)malonate [77] was isolated in the form of amber crystals. These crystals were dissolved and filtered to remove any salts and then refluxed overnight with sodium metal. After purification using radial chromatography ethyl α -(hexahydro pyridylidene-2)acetate [69] was obtained as a clear liquid in an overall yield of 24%. This was confirmed by ¹³C and ¹H NMR spectroscopic data. Meldrum's acid and isopropylidene α -(hexahydro-2-pyridinylidene)malonate [77] were also recovered.



Scheme 3.10 (i) DMS, 60 °C; (ii) Meldrum's acid, Et₃N, toluene, reflux; (iii) NaOEt, EtOH, reflux.

3.5 Synthesis of the cyclopentenone moiety

To synthesise the cyclopentenone moiety of the molecule for the convergent synthesis outlined in Scheme 3.7, simple propargyl compounds would be used as starting materials. Norbornadiene was again used as the alkene of choice for the initial reactions. The Pauson-Khand reaction was attempted on propargyl bromide [78] and propargyl alcohol [63] [Scheme 3.11]. The alkynes were added respectively to dichloromethane and placed under nitrogen. Then dicobalt octacarbonyl was introduced to form the intermediate alkyne-cobalt complex. The reaction mixture evolved carbon dioxide. After stirring at ambient temperature the reaction mixture was cooled and norbornadiene was injected into the reaction vessel and NMO was added to promote the reaction. The mixture was allowed to warm to room temperature and left to stir overnight. The reaction with propargyl bromide was unsuccessful and no product was isolated [79]. Starting materials were recovered. However, the reaction with propargyl alcohol was a success and (1*R*,7*S*)-4-(hydroxymethyl) tricyclo [5.2.1.0^{2,6}]deca-4,8-dien-3-one [80] was isolated as a clear liquid



Scheme 3.11 (i) $\text{Co}_2(\text{CO})_8$, norbornadiene, NMO, CH_2Cl_2 .

in 23% yield. The structure was verified by ^{13}C and ^1H NMR spectroscopic data. Full explanation of the signal assignments will be given for the ^1H spectrum but not the ^{13}C spectrum due to the similarities to 1- $\{[(1R,7S)\text{-}5\text{-oxotricyclo}[5.2.1.0^{2,6}]\text{deca-}3,8\text{-dien-}4\text{-yl}\}\text{methyl}\}$ tetrahydro-2(1*H*)-pyridinone [68] which was explained in detail in (Section 3.3).

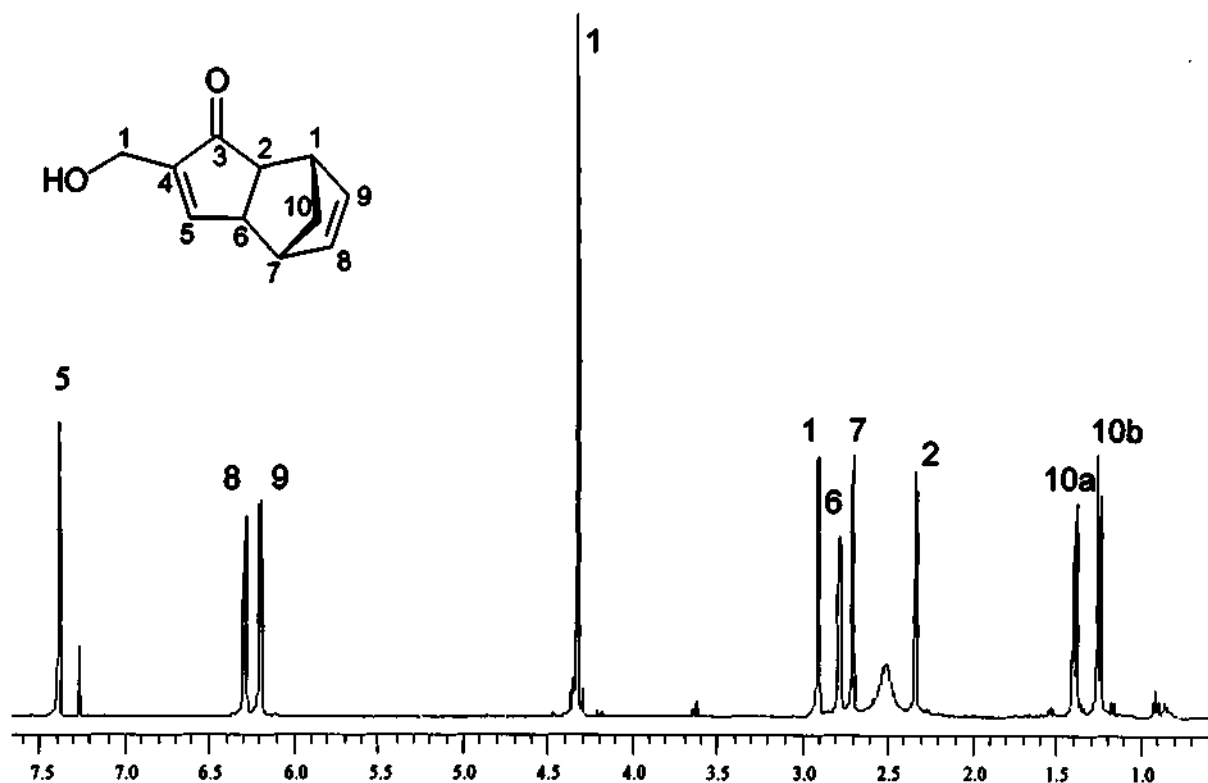
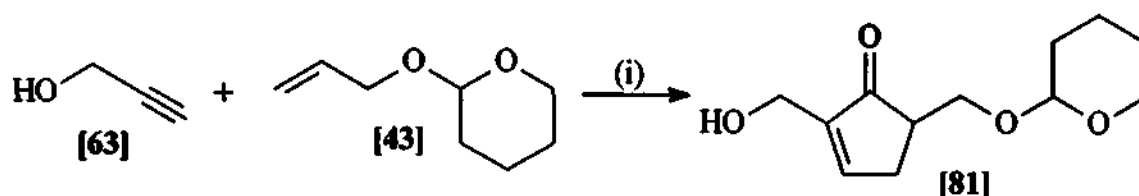


Figure 3.6 ^1H NMR spectrum of (1*R*,7*S*)-4-(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [80]

Integration of the ^1H NMR spectrum [Figure 3.6] showed that all the signals except for the singlet at 4.3 ppm integrate for one proton. Thus the peak at 4.3 ppm must correspond to the proton attached to C_1 . The singlet farthest downfield at 7.4 ppm corresponds to the vinyl proton of C_5 . The multiplets at 6.3 and 6.2 ppm were assigned to the vinyl protons of C_8 and C_9 respectively. The peak at 2.9 ppm was assigned to the proton β to the carbonyl group, C_1 . The next singlet, appearing at 2.8 ppm, was assigned to the proton α to the alkene bond, C_6 . The peak at 2.7 ppm was assigned to the proton which is β to the double bond, namely C_7 . The signal at 2.3 ppm was determined to arise from the proton on C_2 . The doublets at 1.4 and 1.2 ppm were assigned to the two protons of C_{10} . The protons are in sufficiently different magnetic environments to produce two distinct signals. HRMS results produced a mass of 176.08532, which is in good agreement with the calculated mass of 176.08373 a.m.u.

After this encouraging result, the Pauson-Khand reaction was attempted using propargyl alcohol [63] and tetrahydro-2-(2-propenyloxy)pyran [43] (instead of norbornadiene) to try introduce a protected alcohol group [Scheme 3.12]. This is required if a complete synthesis



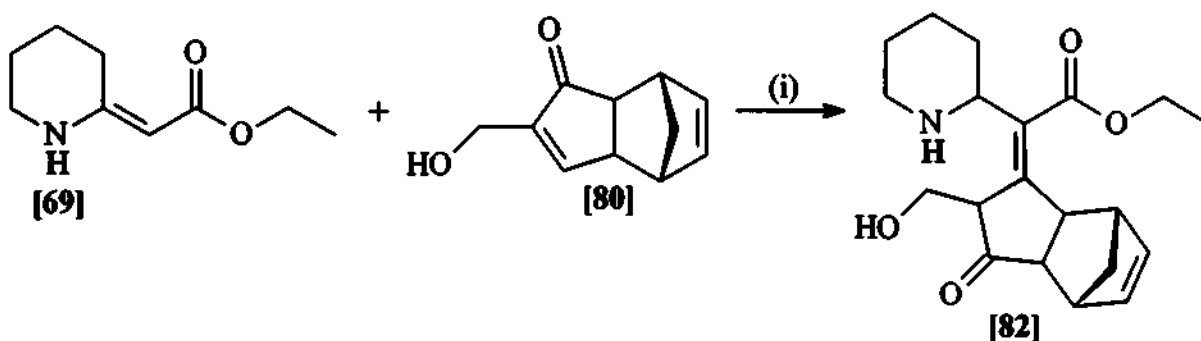
Scheme 3.12 (i) $\text{Co}_2(\text{CO})_8$, norbornadiene, NMO, CH_2Cl_2 .

of alkaloid 251F is to be successful. The same procedure detailed above was followed except the norbornadiene [37] was replaced with tetrahydro-2-(2-propenyloxy)pyran [43]. The reaction was unsuccessful and no product [81] was isolated. Before experimenting with alternative protecting groups we decided to test the efficacy of the methodology for

the remaining reactions. For this purpose we thus proceeded with (1*R*,7*S*)-4-(hydroxymethyl)tricyclo [5.2.1.0^{2,6}]deca-4,8-dien-3-one [80].

3.6 Attempted synthesis of ethyl 2-[4-(hydroxymethyl)-5-oxotricyclo [5.2.1.0^{2,6}]dec-8-en-3-ylidene]-2-(2-piperidiny)acetate [82] (convergent synthesis)

With the two required substituents now prepared the convergent synthesis outlined in Scheme 3.7 could now be attempted. (1*R*,7*S*)-4-(Hydroxymethyl)tricyclo [5.2.1.0^{2,6}]deca-4,8-dien-3-one [80] was dissolved in toluene. Then a slight excess of sodium hydroxide was added to the stirred mixture. After stirring under nitrogen for 5 minutes a near equimolar amount of ethyl α -(hexahydro-2-pyridinylidene)acetate [69] was introduced and the resulting reaction mixture was refluxed for an hour [Scheme 3.13]. After extraction



Scheme 3.13 (i) NaH, toluene, ΔH

with chloroform and removal of the solvent *in vacuo*, TLC and NMR revealed that no product [82] had been formed and no starting materials remained. It appears that the reaction conditions are too harsh for the starting materials with the TLC evidence suggesting that the starting materials decompose during the reaction.

Due to time constraints milder conditions for performing the bonding of (1*R*,7*S*)-4-(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [80] and ethyl α -(hexahydro-2-pyridinylidene)acetate [69] could not be explored. The use of a weaker base is also advisable in case a strong base contributes to the decomposition of the starting materials or possibly the final product.

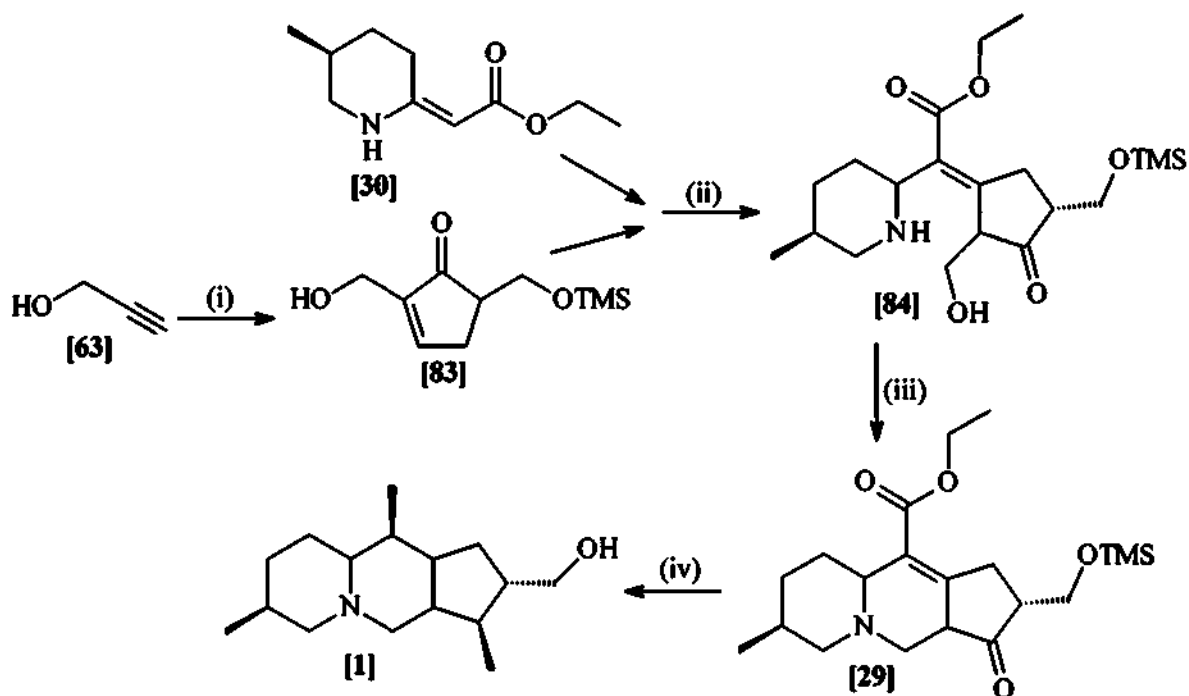
3.7 Conclusion and Future Work

During model studies of the Pauson-Khand reaction it was found that the thiolactam gave consistently higher yields than the lactam. After further investigation it seemed feasible that the sulfur atom of the thiocarbonyl is positioned at a distance where coordination to the cobalt atom could take place. This in turn would stabilize the intermediate complex and thus improve the yield of the reaction.

A new expeditious method of thionating lactams using Lawesson's reagent and microwave energy was used to prepare 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinethione [55] and tetrahydro-2(1*H*)-pyridinethione [65] in high yield after only 20 seconds!

The tactic of using a convergent synthesis to construct frog alkaloid 251F has proved to be the more successful during the course of this work, and should be pursued in any subsequent work. The simple synthesis of ethyl α -(hexahydro-2-pyridinylidene)acetate [70] can be utilised as the basis to construct one moiety [30]. Performing a Pauson-Khand reaction on propargyl alcohol [63] was successful using norbornadiene as the alkene. To obtain the most synthetically exploitable moiety [83] from this reaction, allyl alcohol should be used with the alcohol group either protected to give [83] or unprotected

(depending on which alkene affords the highest yield). The optimisation of this step is vital to obtain a viable yield of product. The investigation of various solvent systems should improve the yield substantially. The bonding of these two moieties to give [84] will require optimisation of the reaction conditions with the use of milder conditions to prevent decomposition of the starting materials. The cyclisation ([84] to [29]) should proceed spontaneously but could require



Scheme 3.14 (i) Pauson-Khand reaction; (ii) Bonding of moieties; (iii) Cyclisation; (iv) Deprotection, introduction of the final methyl group using MeMgBr or MeLi, Functional Group Interconversion and defunctionalisation.

extended heating. Thereafter, the ester functionality will be reduced to the required methyl group and an appropriate Grignard reagent reacted with the ketone to introduce the missing methyl group. Deoxygenation of the tertiary alcohol would complete the synthesis of alkaloid 251F [1].

CHAPTER 4

EXPERIMENTAL

Flash chromatography was performed using either column chromatography with Merck silica gel 60 (230–400 mesh; particle size 0.040–0.063 nm) or by radial chromatography on a chromatotron using Merck silica gel 60 PF₂₅₄, containing gypsum. Thin layer chromatography (TLC) was performed on Merck aluminium sheets coated with silica gel 60 PF₂₅₄ (layer thickness 0.2mm), with visualisation of the compounds by inspection under light (254/365 nm) and/or by exposure to iodine vapour.

NMR spectra were recorded using a 500 MHz Varian Unity Inova spectrometer equipped with an Oxford magnet (11.744T) and a switchable 5mm probe. ¹H NMR spectra were recorded at 500 MHz in deuteriochloroform and referenced against the deuteriochloroform singlet at 7.26 ppm. ¹³C NMR spectra were recorded at 125 MHz in deuteriochloroform and referenced against the central line of the deuteriochloroform triplet at 77.0 ppm. COSY, GHMQC, GHSQC and DEPT spectra were routinely recorded to facilitate the unambiguous assignment of NMR signals. All chemical shift values are given in ppm and coupling constants, *J*, are given in Hz. Spectroscopic data is only given for new compounds. Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

High resolution mass spectra were obtained by the Mass Spectrometry Unit of the Cape Technikon on a double-focusing Kratos MS 80RF mass spectrometer and by Mass Spectrometry Service at the School of Chemistry at the University of the Witwatersrand

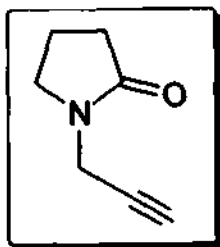
using a Micromass VG 70 SEQ mass spectrometer. Low resolution (Electron Impact) mass spectra were recorded using a ThermoFinnigan Polaris / GCQ Plus instrument. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer Spectrum One spectrometer as thin films between NaCl plates. The absorptions are reported in wave number (cm^{-1}) scale, in the range 400–4000 cm^{-1} . A 700W National domestic microwave oven was used for microwave reactions.

All solvents used for the reactions and preparative chromatography were distilled. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone; acetonitrile, dichloromethane and triethylamine from calcium hydride; toluene from sodium. -78°C temperatures were attained using a dry ice-acetone bath. Great care was taken to ensure moisture sensitive reagents were used under inert conditions. Thus glassware was routinely heated under vacuum and the vacuum replaced with N_2 gas. Concentration or evaporation *in vacuo* refers to the removal of solvent under reduced pressure (9 mmHg, $30\text{--}40^{\circ}\text{C}$) using a rotary evaporator. Yields are calculated from the immediate synthetic precursor used, unless otherwise indicated.

The X-ray data were collected on an Oxford Diffraction Xcalibur 2 CCD diffractometer at $-173(1)^{\circ}\text{C}$ at an X-ray power of 2.0 kW (Mo K α radiation). Lorentz, scan speed scaling, and overlap corrections were applied during data reduction with the program CrysAlis RED. The structure was solved in the monoclinic space group $P2_1/n$ using direct methods (SHELXS-97)^{55a} and refined anisotropically (SHELXL-97)^{55b} to a final R_1 of 3.94%. The programs ORTEP,⁵⁶ WinGX,⁵⁷ Mercury 1.1,⁵⁸ and Oscale⁵⁹ were used for data analysis and graphics.

4.1 Pauson-Khand reactions of 1-(2-propynyl)tetrahydro-2H-pyrrol-2-one [38] with various alkenes

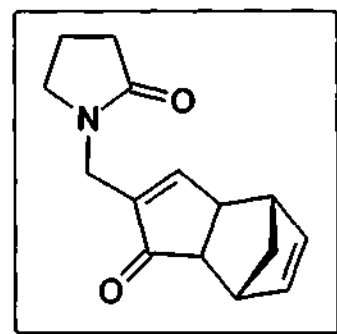
4.1.1.1 Synthesis of 1-(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39]



Sodium hydride (50% suspension in mineral oil, 2.03 g, 42.3 mmol) was added to a solution of propargyl bromide (80% solution in toluene, 4.7 ml, 42.3 mmol) and pyrrolidine-2-one (2.7 ml, 35.3 mmol) in dry THF (50 ml) at 0°C. The resulting reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched by the addition of water (100 ml) and the organic components extracted with ethyl acetate (3 x 100 ml). The organic extracts were dried (MgSO₄), filtered and then evaporated *in vacuo*. Purification by chromatography (3:1 hexane – ethyl acetate as eluent) afforded 1-(2-propynyl)tetrahydro-2H-pyrrol-2-one [38] (3.20 g, 74%) as a yellow oil ; R_f (1:1 hexane – ethyl acetate) 0.34; *m/z* 124. The spectroscopic data were in close agreement with those of reported by Gravestock and Peirson.⁴⁶

4.1.1.2 Using norbornadiene as alkene

Dicobalt octacarbonyl (1.1 equivalents, 541 mg, 1.58 mmol) was added in one portion to a solution of 1-(2-propynyl)tetrahydro-2H-pyrrol-2-one [39] (175 mg, 1.42 mmol) and dichloromethane (7 ml) and stirred at room temperature for half an hour. The reaction mixture was then cooled to 0°C

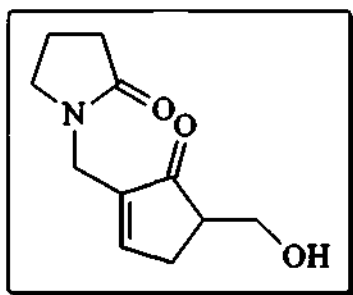


before norbornadiene (10 equivalents, 1.53 ml, 14.2 mmol) and the promoter, *N*-methyl

morpholine *N*-oxide (NMO) (6 equivalents, 998 mg, 8.52 mmol) were introduced to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left to stir overnight. The reaction mixture was then washed through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:3 ethyl acetate – hexane) to obtain 1{[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}-2-pyrrolidinone [44] (148 mg, 42% yield) as white crystals; *R*_F (1:1 ethyl acetate – hexane) 0.08; melting point 89-91°C; *ν*_{max} (KBr) 2974 (s, =C-H), 1683 (m, C=O), 1626 (m, C=C), 1376 (m, C-N), 722 (C-H out-of-plane bending) cm⁻¹; *δ*_H (CDCl₃) 7.28 (1H, s, CH=CCO), 6.22 (1H, dd, *J* 5.5, 2.7 Hz, CHCH(CH₂)CHCH), 6.14 (1H, dd, *J* 5.5, 2.7 Hz, CHCH(CH₂)CHCO), 3.95 (2H, s, NCH₂CCO), 3.34 (2H, m, NCH₂CH₂), 2.84 (1H, s, CH(CH₂)CHCO), 2.70 (1H, s, CHCH=C), 2.64 (1H, s, CH(CH₂)CHCH=C), 2.32 (2H, t, *J* 8.2 Hz, CH₂CO), 2.26 (1H, d, *J* 5.5 Hz, CHCO), 1.97 (2H, dd, *J* 8.2, 7.3 Hz, CH₂CH₂N), 1.32 (1H, d, *J* 9.1 Hz, -CH₂H-CH), 1.12 (1H, d, *J* 9.1 Hz, -CHH₂CH); *δ*_C (CDCl₃) 208.6 (CC=O), 175.0 (NC=O), 161.6 (CHCH=C), 145.1 (CH=CC=O), 138.3 (CHCH(CH₂)CHCH=C), 136.8 (CHCH(CH₂)CHC=O), 52.6 (CHCHC=O), 47.7 (CHCH=C), 47.6 (CH₂NC=O), 43.4 (CH(CH₂)CHC=O), 42.7 (CH(CH₂)CHCH=C), 41.0 ((CH₂)CHCHC=O), 37.4 (C=OCCH₂N), 30.5 (NC=OCH₂CH₂CH₂), 17.8 (NCH₂CH₂CH₂C=O); *m/z* 244 (8%, M⁺+1), 243 (55%, M⁺), 178 (100), 158 (88), 98 (34), 93 (41) (Found: M⁺ - H, 243.1259. C₁₅H₁₇O₂N requires 243.1250).

4.1.2 Using allyl alcohol [41] as alkene

1-(2-Propynyl)tetrahydro-2*H*-pyrrol-2-one [39] (100 mg, 0.812 mmol) was dissolved in dichloromethane (7 ml) and dicobalt octacarbonyl (1.1 equivalents, 305 mg, 0.893 mmol)

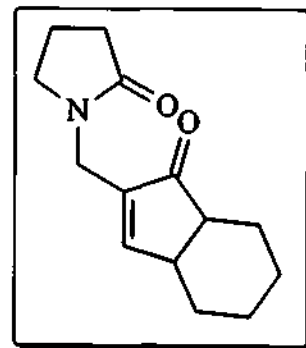


was added in one portion to the solution which was left to stir at room temperature for half an hour. The reaction mixture was then cooled to 0°C before allyl alcohol (10 equivalents, 0.46 ml, 8.12 mmol) and the promoter, NMO (6 equivalents, 571 mg, 4.87 mmol) were added to the reaction mixture. The

reaction mixture was then allowed to warm to ambient temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO_4), concentrated *in vacuo* and purified using radial chromatography (1:3 ethyl acetate – hexane). Starting materials were recovered and an unidentifiable by-product obtained but the desired product was not produced.

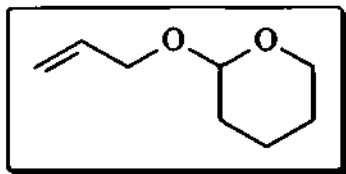
4.1.3 Using cyclohexene [42] as alkene

1-(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39] (100 mg, 0.812 mmol) was dissolved in dichloromethane (7 ml) and dicobalt octacarbonyl (1.1 equivalents, 305 mg, 0.893 mmol) was added in one portion to the solution. This solution was stirred at room temperature for half an hour. The reaction mixture was then



cooled to 0°C and cyclohexene (10 equivalents, 0.73 ml, 8.12 mmol) and NMO (6 equivalents, 571 mg, 4.87 mmol) were added. The reaction mixture was then allowed to warm to ambient temperature and left stirring overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO_4), concentrated *in vacuo* and purified using radial chromatography (1:3 ethyl acetate – hexane). No product was formed and starting materials were recovered.

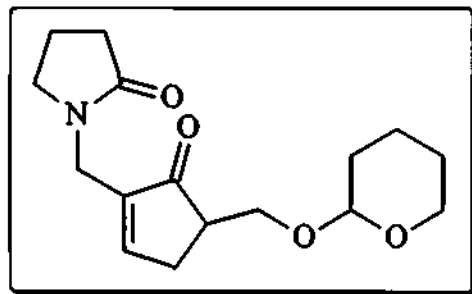
4.1.4.1 Synthesis of tetrahydro-2-(propenyloxy)pyran [43]



A solution of allyl alcohol (29 g, 0.50 mol), dihydropyran (50.4 g, 0.601 mol), and toluene-*p*-sulfonic acid (10 mg, 0.05 mmol) in dichloromethane (150 ml) was stirred at room temperature for 15 hours. The solution was washed with saturated NaHCO₃ solution (50 ml) and brine (50 ml), dried (MgSO₄) and fractionally distilled to give tetrahydro-2-(propenyloxy)pyran (60.0g, 0.425 mol, 85%) as a colourless oil: bp (61-62 °C /15 mmHg) lit. (60-63 °C 15 mmHg).⁴⁰

4.1.4.2 Using tetrahydro-2-(propenyloxy)pyran [43] as alkene

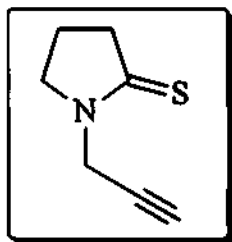
Dicobalt octacarbonyl (1.1 equivalents, 610 mg, 1.78 mmol) was added in one portion to a solution of 1-(2-Propynyl)tetrahydro-2*H*-pyrrol-2-one [39] (200 mg, 1.62 mmol) dissolved in dichloromethane (7 ml) and was left to stir at room temperature for



half an hour. The reaction mixture was cooled to 0°C before tetrahydro-2-(propenyloxy)pyran [43] (10 equivalents, 1 ml, 16.2 mmol) and the promoter, NMO (6 equivalents, 1.14 g, 9.74 mmol) were added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane). Starting materials were recovered but the desired product was not obtained.

4.2 Pauson-Khand reactions of 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [40] with various alkenes

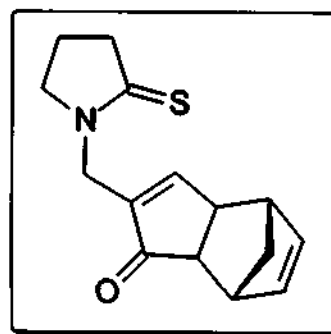
4.2.1.1 Synthesis of 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [40]



Sodium carbonate (3.82 g, 36.0 mmol) was added to a suspension of phosphorus pentasulfide (16.0 g, 36.0 mmol) in dry THF (150 ml). The reaction mixture was stirred until it had become homogeneous (20-30 min). 1-(2-Propynyl)tetrahydro-2H-pyrrol-2-one [39] (3.70 g, 30.0 mmol) was added and the mixture stirred at room temperature. The progress of the reaction was monitored by TLC. The reaction was quenched by the addition of aqueous trisodium phosphate (10% w/w, 100 ml). The organic components were extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried (MgSO_4), filtered and the solvents evaporated *in vacuo* to afford 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione (3.65 g, 26.1 mmol, 87%) as an orange oil after column chromatography (hexane – ethyl acetate 3:1 as eluent); R_F (3:1 hexane – ethyl acetate) 0.25; m/z 139. The spectroscopic data were in close agreement with those of reported by Gravestock and Peirson.⁴⁶

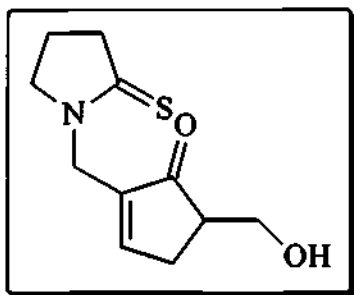
4.2.1.2 Using norbornadiene [37] as alkene

Dicobalt octacarbonyl (1.1 equivalents, 540 mg, 1.58 mmol) was added in one portion to a solution of 1-(2-propynyl)tetrahydro-2H-pyrrole-2-thione [40] (200 mg, 1.44 mmol) and dichloromethane (7 ml) and stirred at room temperature for half an hour. The reaction mixture was then



cooled to 0°C before norbornadiene (10 equivalents, 0.9 ml, 14.4 mmol,) and NMO (6 equivalents, 1.01 g, 8.64 mmol) were introduced to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left stirring overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:2 ethyl acetate – hexane) to obtain (1*R*,7*S*)-4-[(2-thioxo-1-pyrrolidinyl)methyl]tricyclo [5.2.1.0^{2,6}]deca-4,8-dien-3-one [49] (231 mg, 0.89 mmol, 62% yield) as white crystals; R_F (1:1 ethyl acetate – hexane) 0.32; melting point 91-92°C; ν_{max} (film) 2925 (s, =C-H), 1460 (s, C=S), 1377 (m, C=C), 1306 (s, C-N), 722 (C-H out-of-plane bending) cm⁻¹; δ_{H} (CDCl₃) 7.22 (1H, s, CH=CCO), 6.28 (1H, dd, J 5.5, 2.7 Hz, CHCH(CH₂)CHCH), 6.20 (1H, dd, J 5.5, 2.7 Hz, CHCH(CH₂)CHCO), 4.07 (2H, m, NCH₂CH₂CH₂CS), 3.91 (2H, s, NCH₂CCO), 3.42 (2H, t, J 8.2 Hz, CH₂CS), 2.90 (1H, s, CH(CH₂)CHCO), 2.76 (1H, s, CHCH=C), 2.68 (1H, s, CH(CH₂)CHCH=C), 2.32 (1H, d, J 5.5 Hz, CHCO), 1.97 (2H, dd, J 8.2, 7.3 Hz, SCH₂CH₂CH₂N), 1.39 (1H, d, J 9.1 Hz, -CH₂H-CHCHCO), 1.23 (1H, d, J 9.1 Hz, -CHH₂CH); δ_{C} (CDCl₃) 208.7 (CC=O), 201.0 (NC=S), 163.7 (CHCH=C), 142.9 (CH=CC=O), 138.3 (CHCH(CH₂)CHCH=C), 136.8 (CHCH(CH₂)CHC=O), 55.6 (CHCHC=O), 52.4 (CH₂NC=S), 47.9 (CHCH=C), 43.5 (CH(CH₂)CHC=O), 42.7 (CH(CH₂)CHCH=C), 42.4 (NC=SCH₂), 41.1 ((CH₂)CHCHC=O), 34.7 (C=OCCH₂N), 19.6 (NCH₂CH₂CH₂C=S); *m/z* 260 (4%, M⁺ +1), 259 (26%, M⁺), 193 (100), 165 (81), 164 (14), 160 (13), 139 (14), 97 (12) (Found: M⁺ - H, 259.1031. C₁₅H₁₇ONS requires 259.1023).

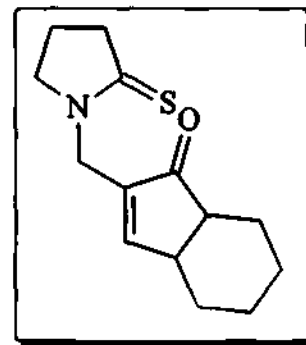
4.2.2 Using allyl alcohol as alkene



1-(2-Propynyl)tetrahydro-2*H*-pyrrole-2-thione [40] (200 mg, 1.44 mmol) was dissolved in dichloromethane (7 ml) and dicobalt octacarbonyl (1.1 equivalents, 540 mg, 1.584 mmol) was added in one portion to the solution which was left to stir at room temperature for half an hour. The reaction mixture was then cooled to 0°C before allyl alcohol (10 equivalents, 0.98 ml, 14.4 mmol) and NMO (6 equivalents, 1.01 g, 8.64 mmol) were added to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane). 5-(hydromethyl)-2-[(2-thioxo-1-pyrrolidinyl) methyl]-2-cyclopenten-1-one (32 mg, 0.14 mmol, 10% yield) was afforded as a yellow oil; *R_F* (1:1 ethyl acetate – hexane) 0.32; *ν*_{max} (film) 2925 (s, =C-H), 1462 (s, C=S), 1377 (m, C=C), 1306 (s, C-N), 722 (C-H out-of-plane bending) cm⁻¹; *δ*_H (CDCl₃) 7.26 (1H, s, CH=CC=O), 4.52 (2H, s, CCH₂NC=S), 3.92 (2H, m, HOCH₂CHC=O), 3.76 (2H, m, CHCH₂CH=C), 3.02 (2H, t, *J* 7.5, 8.1 Hz, CH₂CH₂CH₂NC=S), 2.63 (1H, m, OHCH₂CHCO), 2.51 (2H, d, *J* 19.3 Hz, NCH₂CH₂CH₂C=S), 2.04 (2H, m, NCH₂CH₂CH₂C=S); *δ*_C (CDCl₃) 210.3 (CC=O), 201.8 (NC=S), 162.9 (CHCH=C), 139.0 (CH=CC=O), 62.4 (C=OCHCH₂OH), 55.7 (O=CCHCH₂CHC), 47.2 (CH₂CHC=O), 44.7 (C=SCH₂CH₂CH₂N), 42.1(NCH₂CC=O), 30.6 (C=SCH₂CH₂CH₂N), 19.7 (C=SCH₂CH₂CH₂N); *m/z* 226 (6%, *M*⁺ +1), 225 (34%, *M*⁺), 197 (7), 166 (10), 152 (12), 140 (13), 139 (100), 102 (14), 85 (12) (Found: *M*⁺ - H, 225.08235. C₁₁H₁₅O₂NS requires 225.08268).

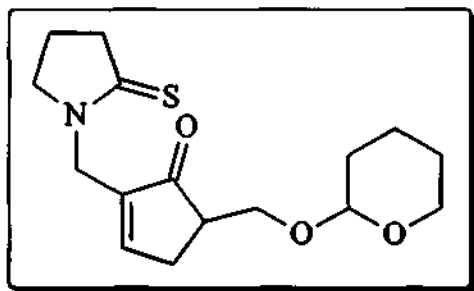
4.2.3 Using cyclohexene [42] as alkene

1-(2-Propynyl)tetrahydro-2*H*-pyrrole-2-thione [40] (100 mg, 0.718 mmol) was dissolved in dichloromethane (7 ml) and dicobalt octacarbonyl (1.1 equivalents, 270 mg, 0.790 mmol) was added in one portion to the solution. The mixture was left stirring at ambient temperature for half an hour. The reaction mixture



was then cooled to 0°C before cyclohexene (10 equivalents, 0.73 ml, 7.182 mmol) and NMO (6 equivalents, 505 mg, 4.31 mmol) were added to the reaction mixture. The reaction mixture was then allowed to warm to room temperature and left to stir overnight. The reaction mixture was then washed through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane). 2-[(2-Thioxo-1-pyrrolidinyl)methyl]-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (22 mg, 0.086 mmol, 12% yield) was afforded as a yellow oil; *R*_F (1:1 ethyl acetate – hexane) 0.08; *v*_{max} (film) 2922 (s, =C-H), 1463 (s, C=S), 1377 (m, C=C), 1306 (s, C-N), 722 (C-H out-of-plane bending) cm⁻¹; δ_H (CDCl₃) 7.26 (1H, s, CH=CCO), 4.50 (2H, m, CH=CCH₂N), 4.03 (2H, m, NCH₂CH₂CH₂), 3.76 (1H, m, C=OCH(CH)CH₂CH₂), 3.65 (1H, m, C=CHCH(CH)CH₂CH₂), 3.02 (4H, m, COCHCH₂CH₂CH₂CH₂CH, COCHCH₂CH₂CH₂CH₂CH), 2.92 (2H, m, C=CCH(CH)CH₂CH₂), 2.63 (2H, d, *J* 19.3 Hz, NC=SCH₂CH₂), 2.06 (2H, m, C=SCH₂CH₂CH₂N), 1.24 (2H, m, COCH(CH)CH₂CH₂); δ_C (CDCl₃) 207.8 (CC=O), 203.0 (NC=S), 161.7 (CHCH=C), 138.6 (CH=CC=O), 55.9 (C=OCH(CH)CH₂CH₂), 55.5 (C=CHCH(CH)CH₂CH₂), 48.2 (CH₂CH₂N), 44.9 (C=CHCH(CH)CH₂CH₂), 44.7 (C=OCH(CH)CH₂CH₂), 43.6 (C=CHCHCH₂CH₂), 42.5 (CH=CCH₂N), 31.7 (C=SCH₂CH₂CH₂N), 29.6 (C=OCH(CH)CH₂CH₂), 19.6 (C=SCH₂CH₂CH₂N); *m/z* 249. Compound decomposed before HRMS analysis could be performed.

4.2.4 Using tetrahydro-2-(propenyloxy)pyran [43] as alkene



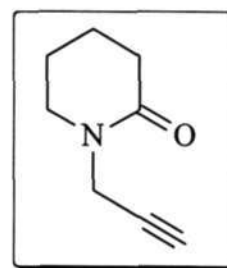
Dicobalt octacarbonyl (1.1 equivalents, 809 mg, 2.37 mmol) was added in one portion to a solution of 1-(2-propynyl)tetrahydro-2H-pyrrol-2-thione [40] (300 mg, 2.15 mmol) dissolved in dichloromethane (7 ml) and was left to stir at room temperature for

half an hour. The reaction mixture was cooled to 0°C before tetrahydro-2-(propenyloxy)pyran [43] (10 equivalents, 1.2 ml, 21.5 mmol) and the promoter, NMO (6 equivalents, 1.52 g, 12.9 mmol) were added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane) to obtain 5-[(tetrahydro-2H-pyran-2-yloxy)methyl]-2-[(2-thioxo-1-pyrrolidinyl) methyl]-2-cyclopenten-1-one [52] (63.4 mg, 0.215 mmol, 10% yield) as a yellow oil; *R_F* (1:1 ethyl acetate – hexane) 0.25; *ν*_{max} (film) 2926 (s, =C-H), 1461 (s, C=S), 1377 (m, C=C), 1305 (s, C-N), 722 (C-H out-of-plane bending) cm⁻¹; *δ*_H (CDCl₃) 7.26 (1H, s, CH=CCO), 4.51 (2H, m, C=OCCH₂N), 4.04 (2H, d, *J* 5.5 Hz, OCCHCH₂O), 3.90 (2H, d, *J* 7.5 Hz, C=CHCH₂CH(CH)CO), 3.03 (2H, m, NCH₂CH₂CH₂C=S), 2.81 (1H, d, *J* 19.2 Hz, COCH(O)CH₂CH₂), 2.64 (2H, d, *J* 6.8 Hz, OCCH(CH₂)CH₂CH=C), 2.40 (2H, m, C=SCH₂CH₂CH₂N), 2.07 (2H, m, C=SCH₂CH₂CH₂N), 1.54 (2H, s, OCH₂CH₂CH₂CH₂CH), 1.25 (4H, s, OCH₂CH₂CH₂CH₂CH, OCH₂CH₂CH₂CH₂CH), 0.88 (2H, m, OCH₂CH₂CH₂CH₂CH); *δ*_C (CDCl₃) 207.8 (CC=O), 203.0 (NC=S), 161.8 (CH₂CH=C), 138.6 (CH=CC=O), 55.9 (COCH(CH₂)CH₂CH=C), 55.5 (COCH(CH₂)CH₂O), 48.2 (NCH₂CH₂CH₂C=S), 44.9 (OCH₂CH₂CH₂CH₂CHO), 43.6

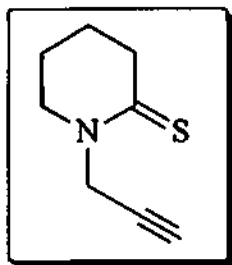
(COCH(CH₂)CH₂CH=C), 42.6 (CH=CCH₂N), 31.8 (NCH₂CH₂CH₂C=S), 29.7 (OCH₂CH₂CH₂CH₂CHO), 29.6 (OCH₂CH₂CH₂CH₂CHO), 22.6 (OCH₂CH₂CH₂CH₂CHO), 19.8 (NCH₂CH₂CH₂C=S), 14.1 (OCH₂CH₂CH₂CH₂CHO); *m/z* 308. Compound decomposed before HRMS analysis could be performed

3.2 Synthesis of 1-(2-propynyl)tetrahyrdro-2(1*H*)-pyridinone [54]

Sodium hydride (50% suspension in mineral oil, 2.03 g, 42.3 mmol) was added to dry THF (50 ml) and cooled to -78°C in a acetone/dry ice bath. δ-Valerolactam (3.50 g, 35.3 mmol) was then added to the suspension and stirred for 15 minutes. Then propargyl bromide (80% solution in toluene, 4.7 ml, 42.3 mmol) was injected into the solution. The resulting reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched by the addition of water (100 ml) and the organic components extracted with ethyl acetate (3 x 100 ml). The organic extracts were dried (MgSO₄), filtered and then concentrated *in vacuo*. Purification by radial chromatography (1:1 hexane – ethyl acetate as eluent) afforded 1-(2-propynyl)tetrahyrdro-2(1*H*)-pyridinone [54] (3.14 g, 23.0 mmol, 65%) as a yellow oil ; *R_F* (1:1 hexane – ethyl acetate) 0.36; *m/z* 138; δ_H (CDCl₃) 4.12 (2H, s, NCH₂C≡CH), 3.31 (2H, t, J 6.2, 5.6, C=ONCH₂CH₂), 2.28 (2H, t, J 6.8, 6.2, NC=OCH₂CH₂), 2.22 (1H, t, J 2.5, CH≡CCH₂N), 1.74 (2H, m, NCH₂CH₂CH₂CO), 1.70 (2H, m, COCH₂CH₂CH₂N); δ_C (CDCl₃) 169.3 (NC=O), 78.5 (CH≡CCH₂N), 71.4 (CH≡CCH₂N), 46.9 (C=ONCH₂CH₂), 35.2 (NCH₂C≡CH), 32.0 (NC=OCH₂CH₂), 22.7 (NCH₂CH₂CH₂CH₂C=O), 21.0 (C=OCH₂CH₂CH₂CH₂N). All spectroscopic data corresponded closely to that quoted by Wei and co-workers.⁴⁵



3.3 Attempted synthesis of 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [55]



Sodium carbonate (3.82 g, 36.0 mmol) was added to a suspension of phosphorus pentasulfide (16.0 g, 36.0 mmol) in dry THF (150 ml). The reaction was stirred until it had become homogeneous (20-30 min). 1-(2-Propynyl)tetrahydro-2(1H)-pyridinone [55] (3.70 g, 30.0 mmol) was added and the mixture stirred at room temperature. The progress of the reaction was monitored by TLC. The reaction was quenched by the addition of aqueous trisodium phosphate (10% w/w, 100 ml). The organic components were extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. None of the desired product was obtained.

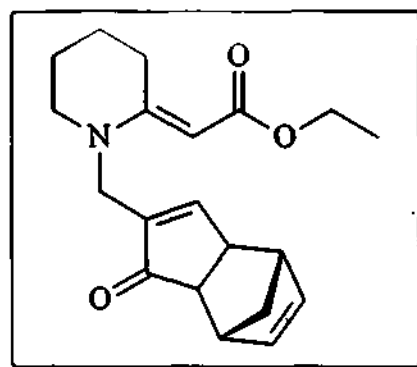
3.4 Alternative synthesis of 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [55]

The thionation was then carried out using microwave irradiation. 1-(2-Propynyl)tetrahydro-2(1H)-pyridinone [54] (200 mg, 1.45 mmol) and Lawesson's reagent (290 mg, 0.725 mmol) were mixed together in a polytop vial was placed on a bed of alumina, which was placed in the microwave. The mixture was then heated for twenty seconds on the low power setting. The material was then extracted with dichloromethane and purified by radial chromatography (1:1 hexane – ethyl acetate as eluent) afforded 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione (138 mg, 1.02 mmol, 70%) as a yellow oil ; *R_F* (1:1 hexane – ethyl acetate) 0.61; *m/z* 138; δ_{H} (CDCl₃) 4.04 (2H, s, NCH₂C≡CH), 3.23 (2H, t, J 6.2, 5.6, C=ONCH₂CH₂), 2.22 (2H, t, J 6.8, 6.2, NC=OCH₂CH₂), 2.09 (1H, t, J 2.5, CH≡CCH₂N), 1.68 (2H, m, NCH₂CH₂CH₂CO), 1.64 (2H, m, COCH₂CH₂CH₂N); δ_{C} (CDCl₃) 200.1 (NC=S), 78.3 (CH≡CCH₂N), 72.7 (CH≡CCH₂N), 49.6 (C=SNCH₂CH₂),

43.0 (NCH₂C≡CH), 41.2 (NC=OCH₂CH₂), 22.3 (NCH₂CH₂CH₂CH₂C=O), 20.1 (C=OCH₂CH₂CH₂CH₂N); This compound is extremely unstable and decomposed rapidly under all conditions. Hence no HRMS or IR analysis could be performed.

3.5 Attempted synthesis of ethyl 2-(1-((1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl)methyl)-2-piperidinylidene)acetate [56]

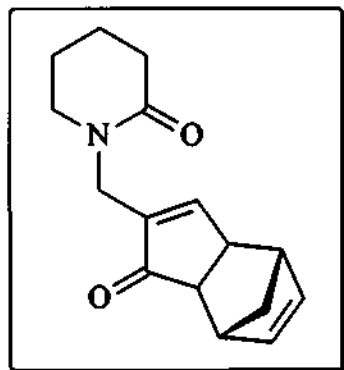
1-(2-Propynyl)tetrahydro-2(1*H*)-pyridinone (200 mg, 1.45 mmol) was mixed with Lawesson's reagent (290 mg, 0.725 mmol) in a polytop vial and heated in the microwave oven for 20 seconds on low. This process was repeated so two batches of product were produced.



These were extracted with dichloromethane, combined, filtered and immediately dissolved in dichloromethane (7 ml) and placed under a nitrogen atmosphere. Dicobalt octacarbonyl (1.1 equivalents, 1.09 g, 3.18 mmol) was added in one portion the solution of 1-(2-propynyl)tetrahydro-2*H*-pyrrole-2-thione (~ 400 mg, 2.9 mmol) and stirred at room temperature for half an hour. The reaction mixture was then cooled to 0°C before norbornadiene (10 equivalents, 1.8 ml, 29.2 mmol) and NMO (6 equivalents, 2.03 g, 17.4 mmol) were introduced to the reaction mixture. The reaction mixture is then allowed to warm to ambient temperature and left stirring overnight. The reaction mixture was then rapidly filtered through a silica gel plug with ethyl acetate. The extract was concentrated *in vacuo*. Formation of the α -thiominium salt was achieved using ethyl bromoacetate (1.5 equivalents, 0.49 ml, 4.34 mmol) added dropwise to a solution of the extract and acetonitrile (5 ml) and monitored using TLC. Once maximum salt formation had occurred triethylamine (1.5 equivalents, 0.6 ml, 4.34 mmol) and triphenylphosphine (1.5

equivalents, 1.14 g, 4.34 mmol) dissolved in dichloromethane (2.5 ml) were introduced. No product was obtained and no starting materials were recovered.

3.6 Synthesis of 1-[[[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}tetrahydro-2(1*H*)-pyridinone [68]

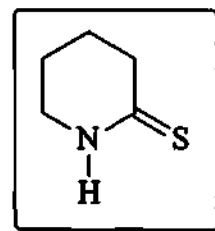


Dicobalt octacarbonyl (1.1 equivalents, 816 mg, 2.39 mmol) was added in one portion to a solution of 1-(2-propynyl)tetrahydro-2(1*H*)-pyridinone [54] (300 mg, 2.17 mmol) and dichloromethane (7 ml) and stirred at room temperature for half an hour. The reaction mixture was then cooled to 0°C before norbornadiene (10 equivalents, 2.31 ml, 21.7 mmol,) and NMO (6 equivalents, 1.525 g, 13.02 mmol) were added to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left stirring overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane) to obtain 1-[[[(1*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-yl]methyl}tetrahydro-2(1*H*)-pyridinone [68] (133 mg, 24% yield) as a transparent oil; *R*_F (1:1 ethyl acetate – hexane) 0.08; *ν*_{max} (KBr) 2949 (s, =C-H), 1697 (s, C=S), 1631 (m, C=C), 1494 (s, C-N), 712 (C-H out-of-plane bending) cm⁻¹; *δ*_H (CDCl₃) 7.31 (1H, s, CH=CCO), 6.25 (1H, dd, *J* 5.5, 2.7 Hz, CHCH(CH₂)CHCH), 6.16 (1H, dd, *J* 5.5, 2.7 Hz, CHCH(CH₂)CHCO), 4.07 (2H, s, NCH₂CCO), 3.32 (2H, m, *J* 9.2, 7.3, 6.4, 2.7, Hz, NCH₂CH₂CH₂CH₂CO), 2.87 (1H, s, CH(CH₂)CHCO), 2.72 (1H, s, CHCH=C), 2.66 (1H, s, CH(CH₂)CHCH=C), 2.34 (2H, t, *J* 8.2 Hz, CH₂CH₂CON), 2.28 (1H, d, *J* 5.5 Hz, CHCO), 1.80-1.65 (2 x 2H, m, COCH₂CH₂CH₂CH₂N), 1.34 (1H, d, *J* 9.1

Hz, $-\text{CH}_a\text{H}-\text{CHCHCO}$), 1.15 (1H, d, J 9.1 Hz, $-\text{CHH}_b\text{CHCHCO}$); δ_c (CDCl_3) 209.1 ($\text{CC}=\text{O}$), 161.7 ($\text{CHCH}=\text{C}$), 145.7 ($\text{CH}=\text{CC}=\text{O}$), 138.4 ($\text{CHCH}(\text{CH}_2)\text{CHCH}=\text{C}$), 136.9 ($\text{CHCH}(\text{CH}_2)\text{CHC}=\text{O}$), 52.7 ($\text{CHCHC}=\text{O}$), 48.8 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 47.8 ($\text{CHCH}=\text{C}$), 43.5 ($\text{CH}(\text{CH}_2)\text{CHC}=\text{O}$), 42.8 ($\text{CH}(\text{CH}_2)\text{CHCH}=\text{C}$), 42.0 ($(\text{CH}_2)\text{CHCHC}=\text{O}$), 41.1 ($\text{C}=\text{OCCH}_2\text{N}$), 32.3 ($\text{NC}=\text{OCH}_2\text{CH}_2\text{CH}_2$), 23.2 ($\text{NC}=\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 21.2 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{O}$); m/z 257. 258 (43%, $\text{M}^+ + 1$), 257 (23%, M^+), 192 (54), 191 (100), 163 (28), 158 (23), 135 (14), 129 (15), 100 (18) (Found: $\text{M}^+ - \text{H}$, 257.14158. $\text{C}_{16}\text{H}_{19}\text{O}_2\text{NS}$ requires 257.14153).

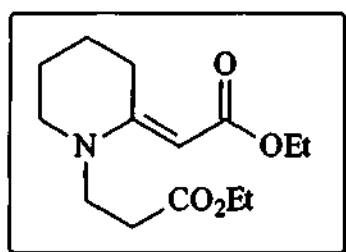
3.7 Tetrahydro-2(1H)-pyridinethione [65]

δ -Valerolactam (400 mg, 4.04 mmol) was mixed with Lawesson's reagent (817 mg, 2.02 mmol) in a polytop vial. The vial was heated in the microwave oven on low power for 20 seconds. The mixture was allowed to cool for a minute and then heated for a further 5 seconds on



low power. The mixture was extracted with dichloromethane (8 ml) and filtered. The extract was dried, concentrated *in vacuo* and then purified using radial chromatography (2:1 ethyl acetate – hexane) to afford tetrahydro-2(1H)-pyridinethione (363 mg, 3.15 mmol, 78%) as a yellow oil; R_F (1:1 ethyl acetate – hexane) 0.37; m/z 115. The spectroscopic data is in close agreement with that reported by Kostir and Padr.⁹⁹

3.8 Ethyl 3-{2-[(E)-2-ethoxy-2-oxoethylidene]piperidino}propanoate [75]

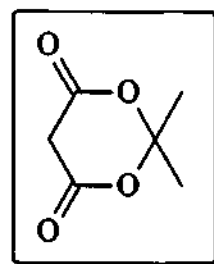


Sodium hydroxide (76 mg, 0.19 mmol) was added to a stirred solution of tetrahydro-2(1H)-pyridinethione (1.08 g, 9.37

mmol) and methyl acrylate (1.7 ml, 18.8 mmol) in wet THF (7 ml). The mixture was allowed to stir for 3 hours at room temperature. The reaction was quenched with water (7 ml) and brine (20 ml). The solution was extracted with ethyl acetate (3 x 10 ml), dried (MgSO_4), filtered and the solvent removed *in vacuo*. This intermediate was dissolved in acetonitrile (5 ml) and ethyl bromoacetate (1.46 ml, 13.1 mmol) was added and left to stir overnight. Salt formation was monitored by TLC. Triphenyl phosphine (2.06 g, 7.87 mmol) and triethylamine (1.10 ml, 7.87 mmol) were dissolved in dichloromethane (~ 2.5 ml) and the mixture added to the acetonitrile solution. The solution was stirred for 2 hours at ambient temperature then quenched with water (10 ml). None of the desired product was isolated.

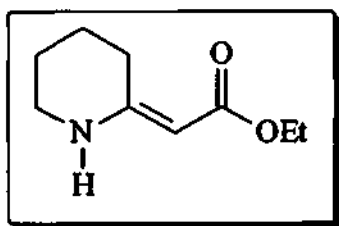
3.9 Isopropylidene malonate (Meldrum's acid)

To a suspension of powdered malonic acid (10.4 g, 0.10 mol) in acetic anhydride (12 ml, 0.12 mol) was added, while stirring, concentrated sulfuric acid (0.3 ml). Acetone (8.0 ml, 0.11 mol) was added to the resulting solution while cooling to maintain the temperature at 20-25°C.



The reaction mixture was allowed to stand in the refrigerator overnight. The resulting crystals were filtered by suction and washed three times with sufficient ice-water to cover the cake then allowed to air-dry. The product was obtained (6.21 g, 82 mmol, 82%) as white crystals. m/z 144. All spectroscopic data were in close agreement of that reported by Davidson and Bernhard.⁴⁹

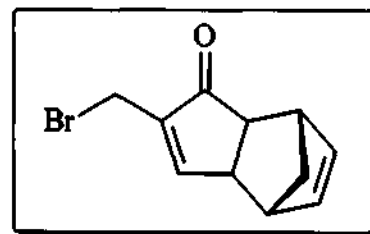
3.10 Ethyl α -(hexahydro piperidylidene-2)acetate [69]



δ -Valerolactam (1 g, 10.1 mmol) was added slowly to dimethyl sulfate (0.96 ml, 10.1 mmol) with stirring under a nitrogen atmosphere. The temperature was maintained at 15°C using a water bath. Once addition was complete the temperature was raised to, and maintained, at 60°C for 16 hours. After cooling, toluene (20 ml) was added to dissolve the product. Meldrum's acid (929 mg, 6.45 mmol) and triethylamine (0.5 ml, 3.59 mmol) were added to the toluene solution and the resulting mixture heated under reflux overnight. The toluene was removed *in vacuo*, replaced with ethanol and filtered to remove any salts. Ethanol was removed *in vacuo*, replaced with absolute ethanol (30 ml) and sodium metal (113 mg) added to form sodium ethoxide *in situ*. The mixture was then heated under reflux overnight. The solvent was removed *in vacuo*, water added (15 ml) and hydrochloric acid (10%) added until the pH measured 6. The resulting mixture was extracted with chloroform (3 x 10 ml), dried (MgSO₄), concentrated *in vacuo* and purified by radial chromatography (1:1 ethyl acetate – hexane) to give ethyl α -(hexahydro piperidylidene-2)acetate (192 mg, 3.23 mmol, 32%) as a clear oil; R_F (1:1 ethyl acetate – hexane) 0.61; m/z 169. All spectroscopic data corresponded closely to that quoted by Maitte and co-workers.⁵²

3.11 (1*R*,7*S*)-4-(Bromomethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [79]

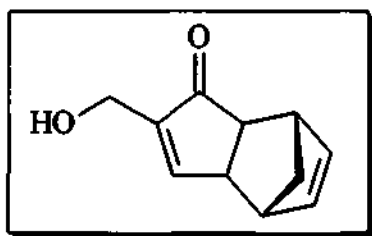
Dicobalt octacarbonyl (1.1 equivalents, 750 mg, 2.19 mmol) was added in one portion to a solution of propargyl bromide (80% solution in toluene, 2.2 mmol, 0.24 ml) dissolved in dichloromethane (7 ml) and was left to stir at room



temperature for half an hour. The reaction mixture was then cooled to 0°C before

norbornadiene (10 equivalents, 1.3 ml, 21.7 mmol) and the promoter, NMO (6 equivalents, 1.53 g, 13.0 mmol) were added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO_4), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane) but the reaction was unsuccessful and no product was isolated.

3.12 (1*S*,7*R*)-4-(Hydroxymethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [80]

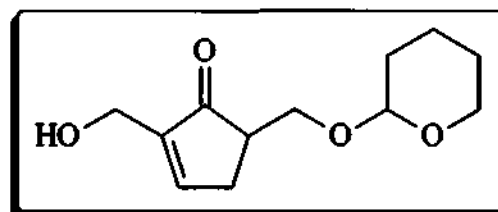


Dicobalt octacarbonyl (1.2 equivalents, 1.00 g, 2.92 mmol) was added in one portion to a solution of propargyl alcohol (0.12 ml, 2.43 mmol) and dichloromethane (5 ml) and stirred at room temperature for half an hour. The reaction mixture was then cooled to 0°C before norbornadiene (10 equivalents, 1.52 ml, 24.3 mmol) and the promoter NMO (6 equivalents, 1.71 g, 14.6 mmol) were introduced to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left to stir overnight. The reaction mixture was then washed through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO_4), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane) to obtain (1*S*,7*R*)-4-(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (51 mg, 0.56 mmol, 23% yield) as a clear oil; R_F (1:1 ethyl acetate – hexane) 0.38; ν_{max} (film) 2946 (s, =C-H), 1460 (s, C=S), 1377 (m, C=C), 1305 (s, C-N), 722 (C-H out-of-plane bending) cm^{-1} ; δ_H (CDCl_3) 7.38 (1H, s, $\text{CH}=\text{CCO}$), 6.28 (1H, dd, J 3.1, 2.5 Hz, $\text{CHCH}(\text{CH}_2)\text{CHCH}$), 6.19 (1H, dd, J 3.1, 2.5 Hz, $\text{CHCH}(\text{CH}_2)\text{CHCO}$), 4.32 (2H, s, HOCH_2CCO), 2.90 (1H, s, $\text{CH}(\text{CH}_2)\text{CHCO}$), 2.77 (1H, s, $\text{CHCH}=\text{C}$), 2.70 (1H, s, $\text{CH}(\text{CH}_2)\text{CHCH}=\text{C}$), 2.33 (1H, d, J 5.0 Hz, CHCO), 1.38 (1H, d,

J 9.3 Hz, $-\text{CH}_2\text{H}-\text{CHCHCO}$), 1.24 (1H, d, J 9.3 Hz, $-\text{CHH}_b\text{CHCHCO}$); δ_c (CDCl_3) 209.9 ($\text{C}=\text{O}$), 160.0 ($\text{CHCH}=\text{C}$), 149.0 ($\text{CH}=\text{CC}=\text{O}$), 138.5 ($\text{CHCH}(\text{CH}_2)\text{CHCH}=\text{C}$), 137.0 ($\text{CHCH}(\text{CH}_2)\text{CHC}=\text{O}$), 57.4 ($\text{HOCH}_2\text{CC}=\text{O}$), 53.2 ($\text{CHCHC}=\text{O}$), 48.1 ($\text{CHCH}=\text{C}$), 43.5 ($\text{CH}(\text{CH}_2)\text{CHC}=\text{O}$), 42.8 ($\text{CH}(\text{CH}_2)\text{CHCH}=\text{C}$), 41.1 ($(\text{CH}_2)\text{CHCHC}=\text{O}$); m/z 176. 177 (33%, $\text{M}^+ + 1$), 176 (27%, M^+), 159 (28), 158 (77), 129 (59), 115 (52), 110 (40), 91 (28), 66 (100), 39 (26) (Found: $\text{M}^+ - \text{H}$, 176.08532. $\text{C}_{11}\text{H}_{12}\text{O}_2$ requires 176.08373).

3.13 2-(Hydroxymethyl)-5-[(tetrahydro-2H-pyran-2-yloxy)methyl]-2-cyclopenten-1-one [81]

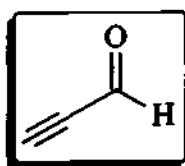
Propargyl alcohol (0.12 ml, 2.43 mmol) was dissolved in dichloromethane (7 ml) and dicobalt octacarbonyl (1.2 equivalents, 1.00 g, 2.92 mmol)



was added in one portion to the solution which was left to stir at room temperature for half an hour. The reaction mixture was then cooled to 0°C before tetrahydro-2-(propenyloxy)pyran (10 equivalents, 24 mmol, 3.4 ml) and the promoter, NMO (6 equivalents, 1.71 mg, 14.6 mmol) were added to the reaction mixture. The reaction mixture was then allowed to warm to ambient temperature and left to stir overnight. The reaction mixture was then filtered through a silica gel plug with ethyl acetate. The resulting organic extract was dried (MgSO_4), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane). The desired product was not produced.

3.14 Alternative synthesis of 1-(2-propynyl)tetrahydro-2(1H)-pyridinethione [55] in from a benzotriazole adduct

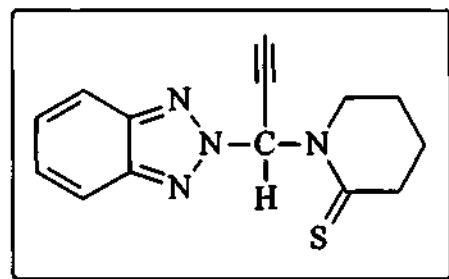
3.14.1 Propynal



A solution of chromium trioxide (30 g, 0.30 mol) in concentrated sulfuric acid (20 ml) and water (60 ml) was added dropwise with stirring over 1 hour to a solution of propynol (propargyl alcohol, 18 g, 0.32 mol) in ethyl methyl ketone (50 ml). The temperature was maintained at 20-25°C by cooling with ice/water. After the mixture had been added, the resulting solution was stirred for 4 hours and diluted with water (15 ml). The organic layer was separated and the aqueous layer was extracted with ether (60 ml). The ether extract and organic layer were combined, dried (MgSO_4) and the solvents were removed *in vacuo*. Distillation at normal atmospheric pressure afforded propynal (15.5 g, 91%, 56-58°C) as a clear oil; (b.p. 55-57°C lit.).⁵¹

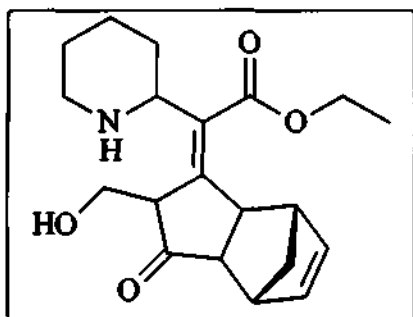
3.14.2 Synthesis of 1-[1-(2*H*-1,2,3-benzotriazol-2-yl)-2-propynyl]tetrahydro-2(1*H*)-pyridinethione [67]

Equimolar amounts of benzotriazole (420 mg, 3.53 mmol), tetrahydro-2(1*H*)-pyridinethione (406 mg, 3.53 mmol) and propynal (0.2 ml, 3.53 mmol) were suspended in toluene (20 ml) and heated under reflux overnight using a Dean-Stark adapter. The intermediate adduct did not form and the net result was that the starting materials were recovered.



3.15 Attempted synthesis of ethyl 2-[4-(hydroxymethyl)-5-oxotricyclo[5.2.1.0^{2,6}]deca-8-en-3-ylidene]-2-(2-piperidinyl)acetate [82]

Ethyl 2-(1-piperidinylidene) acetate (167 mg, 0.989 mmol) was suspended in toluene (5 ml) and stirred at room temperature for 5 minutes with sodium hydroxide (59 mg, 1.23



mmol, 1.1 equivalents) under an inert atmosphere. (1*S*,7*R*)-4-(Hydroxymethyl)tricyclo [5.2.1.0^{2,6}]deca-4,8-dien-3-one (197 mg, 1.12 mmol) was then added and the mixture was heated under reflux, with an inert atmosphere for one hour. The reaction was then

quenched with distilled water and extracted with chloroform (3 x 20 ml). The resulting organic extract was dried (MgSO₄), concentrated *in vacuo* and purified using radial chromatography (1:1 ethyl acetate – hexane). The desired product was not obtained and no starting materials were recovered.

CHAPTER 5

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During the process of attempting to synthesise alkaloid 251F a new expeditious method of thionating lactams with Lawesson's reagent using microwave energy was developed. This method gave the desired lactams in high yield in under 20 seconds!

The idea of using a convergent synthesis to construct frog alkaloid 251F has proved to be the more successful tactic during the course of this work. The synthesis of one of the monomers, namely ethyl α -(hexahydro-2-pyridinylidene)acetate [69] is relatively straightforward and involves the conversion of δ -valerolactam [53] to a lactim ether [76] which is then refluxed with Meldrum's acid. The formation of the complementary monomer was performed utilizing a Pauson-Khand reaction between propargyl alcohol as alkyne, and norbornadiene as alkene. Unfortunately, the coupling of these monomers was unsuccessful. The bonding of these two moieties would require the development of milder reaction conditions to prevent the decomposition of the labile compounds.